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ARYL AND HETEROARYL COMPOUNDS AND METHODS TO  
MODULATE COAGULATION

Statement of Related Application

5       The present application claims priority under 35 USC 119 from the following US  
Provisional Application: Serial Number 60/402,272, filed August 9, 2002, entitled "Aryl and  
Heteroaryl Compounds and Methods to Modulate Coagulation," the entirety of which is  
herein incorporated by reference.

Field of the Invention

10       This invention relates to compounds which are antagonists of the intrinsic clotting  
pathway by binding to and inhibiting the function of factor IX.

Background of the Invention

15       Hemostasis, the arrest of bleeding from an injured blood vessel, requires the  
concerted activity of vascular, platelet, and plasma factors to eventually form a hemostatic  
seal or a blood clot. In normal hemostasis, the combined activity of these factors is  
counterbalanced by regulatory mechanisms to limit the accumulation of platelets and fibrin in  
the area of injury.

20       Upon injury to a blood vessel, vascular factors reduce blood flow from the blood  
vessel by local vasoconstriction and compression of injured vessels. At the same time,  
platelets adhere to the site of vessel wall injury and form aggregates called hemostatic  
plugs, which form the first key element of the hemostatic seal. Platelets also release factors  
that provide surface membrane sites and components for the formation of enzyme/cofactor  
complexes in blood coagulation reactions. Through a series of interacting and propagating  
25       zymogen activations, the activated form of one plasma factor catalyzes the activation of the  
next plasma factor. This cascade of blood coagulation reactions eventually forms a fibrin  
clot. The fibrin clot, an insoluble fibrin matrix that radiates from and anchors the hemostatic  
plug, is the second key element of the hemostatic seal

30       Specifically, the cascade of blood coagulation reactions discussed involve two  
interdependent pathways, an intrinsic pathway and an extrinsic pathway. Each pathway  
ultimately catalyzes the proteolytic activation of factor X to factor Xa.

35       Damage to the blood vessel or a negatively charged surface initiates blood clotting  
by the intrinsic pathway. As seen in Fig. 1, the major components of the intrinsic pathway  
include factor VIII, a non-enzymatic co-factor, and factors IX and XI, zymogen serine  
proteases. The initiation of the intrinsic pathway results in the activation of factor XI to XIa.  
Factor XIa, as well as the presence of the factor VIIa/tissue factor complex involved in the

extrinsic pathway, catalyzes the activation of factor IX to factor IXa. The presence of factor IXa, in combination with the activated form of factor VIII on an appropriate phospholipid surface, results in the formation of a tenase complex (10). The tenase complex catalyzes the formation of factor Xa from its zymogen, factor X.

5       Exposure of blood to injured tissue initiates blood clotting by the extrinsic pathway. As is shown in Fig. 1, the major components of the extrinsic pathway are factor VII, a zymogen serine protease, and tissue factor, a membrane bound protein. Tissue factor serves as the requisite non-enzymatic co-factor for factor VII. The initiation of the extrinsic pathway is thought to be an autocatalytic event resulting from the activation of factor VII by  
10       trace levels of activated factor VII (factor VIIa), both of which are bound to newly exposed tissue factor on membrane surfaces at sites of vascular damage (20). The factor VIIa/tissue factor complex directly catalyzes the formation of factor Xa from factor X.

      Once the initial intrinsic or extrinsic cascade results in the activation of factor X, factor Xa catalyzes the penultimate step in the blood coagulation cascade, the formation of serine  
15       protease thrombin. As seen in Fig. 2, thrombin formation occurs when a prothrombinase complex, comprising of factor Xa, the non-enzymatic co-factor Va and the substrate prothrombin, is assembled on an appropriate phospholipid surface (30).  
      Once formed, thrombin functions as part of a feedback loop, controlling the activation of factors V and VIII. It additionally catalyzes both the activation of factor VIII and the  
20       conversion of fibrinogen to fibrin. Finally, the factor VIIIa interacts with fibrin to catalyze the formation of a thrombus, or crosslinked fibrin clot.

      In normal hemostasis, the process of clot formation (blood coagulation) and clot dissolution (fibrinolysis) is delicately balanced. A slight imbalance between the processes of clot formation and dissolution can lead to excessive bleeding or thrombosis. Many  
25       significant disease states are related to abnormal hemostasis. With respect to the coronary arterial vasculature, abnormal thrombus formation due to the rupture of an established atherosclerotic plaque is the major cause of acute myocardial infarction and unstable angina. Moreover, treatment of an occlusive coronary thrombus by either thrombolytic therapy or percutaneous transluminal coronary angioplasty (PTCA) is often accompanied by an acute  
30       thrombotic reclosure of the affected vessel which requires immediate resolution. With respect to the venous vasculature, a high percentage of patients undergoing major surgery in the lower extremities or the abdominal area suffer from thrombus formation in the venous vasculature which can result in reduced blood flow to the affected extremity and a predisposition to pulmonary embolism. Disseminated intravascular coagulopathy commonly  
35       occurs within both vascular systems during septic shock, certain viral infections and cancer and is characterized by the rapid consumption of coagulation factors and systemic



coagulation which results in the formation of life-threatening thrombi occurring throughout the vasculature leading to widespread organ failure.

Pathogenic thrombosis in the arterial vasculature is a major clinical concern in today's medicine. It is the leading cause of acute myocardial infarction which is one of the leading causes of death in the western world. Recurrent arterial thrombosis also remains one of the leading causes of failure following enzymatic or mechanical recanalization of occluded coronary vessels using thrombolytic agents or percutaneous transluminal coronary angioplasty (PTCA), respectively [Ross, A. M., Thrombosis in Cardiovascular Disorder, p. 327, W.B. Saunders Co. (Fuster, V. and Verstraete, M. edit. 1991); Califf, R. M. and Willerson, J. T., *Id.* at p 389]. In contrast to thrombotic events in the venous vasculature, arterial thrombosis is the result of a complex interaction between fibrin formation resulting from the blood coagulation cascade and cellular components, particularly platelets, which make up a large percentage of arterial thrombi. Heparin, the most widely used clinical anticoagulant administered intravenously, has not been shown to be universally effective in the treatment or prevention of acute arterial thrombosis or rethrombosis [Prins, M. H. and Hirsh, J., *J. Am. Coll. Cardiol.*, 67: 3A (1991)].

Besides the unpredictable, recurrent thrombotic reocclusion which commonly occurs following PTCA, a profound restenosis of the recanalized vessel occurs in 30 to 40% of patients 1 to 6 months following this procedure [Califf, R. M. et al., *J. Am. Coll. Cardiol.*, 17: 2B (1991)]. These patients require further treatment with either a repeat PTCA or coronary artery bypass surgery to relieve the newly formed stenosis. Restenosis of a mechanically damaged vessel is not a thrombotic process but instead is the result of a hyperproliferative response in the surrounding smooth muscle cells which over time results in a decreased luminal diameter of the affected vessel due to increased muscle mass. *Id.* As for arterial thrombosis, there is currently no effective pharmacologic treatment for the prevention of vascular restenosis following mechanical recanalization.

Numerous strategies have been developed for the treatment of thrombotic disorders. Many antithrombotic therapies are based on interference in the hemostatic system. This approach carries the inherent risk of bleeding, since the hemostatic system is no longer fully responsive to potential injury. Therefore, antithrombotic benefits are normally associated with antihemostatic risks. In attempts to improve the benefit-to-risk ratio, antithrombotic agents are continuously being developed. Various antithrombotic strategies include administering general inhibitors of thrombin formation such as heparin or vitamin K antagonists; administering specific thrombin inhibitors; administering specific factor Xa inhibitors; and administering inhibitors of platelet activation and adhesion.

Evaluation of current antithrombotic strategies in terms of antithrombotic benefits versus antihemostatic risks reveals that the benefit-to-risk ratio tends to be more favorable

for strategies that interfere with one specific step rather than in a more general phase of the hemostatic system [L. A. Harker, Biomedical Progress vol 8, 1995, 17-26]. For example, the development of inhibitors specific for factor Xa is an improvement from general and specific thrombin inhibitors. But, this approach still blocks the common (intrinsic and extrinsic) pathway of thrombin generation (see FIG. 1), and thereby thrombin-dependent platelet activation. Thus, a need exists for more specific anti-thrombotic agents that selectively inhibit one single hemostatic pathway, while leaving other pathways unaffected.

#### Summary of the Invention

The present invention provides compositions and methods for the treatment of cardiovascular diseases. More particularly, the present invention relates to modifying thrombus formation and growth by administering an agent or agents that inhibit the clotting activity of factor IX in the intrinsic clotting pathway. Embodiments of the present invention provide compounds of Formula (I) as depicted below. Embodiments of the present invention also provide methods for the preparation of compounds of Formula (I); pharmaceutical compositions comprising compounds of Formula (I); and methods for the use of compounds of Formula (I) and pharmaceutical compositions comprising compounds of Formula (I) in treating human or animal disorders. Compounds of Formula (I) are useful as modulators of the intrinsic clotting pathway by inhibiting the biological activity of factor IX. Compounds of Formula (I) are useful in a variety of applications including management, treatment, control, and/or as an adjunct of diseases in humans caused in part by the intrinsic clotting pathway utilizing factor IX. Such diseases or disease states include cardiopulmonary bypass, stroke, myocardial infarction, deep vein thrombosis associated with surgical procedures or long periods of confinement, acute and chronic inflammation and clotting associated with hemodialysis.

#### Brief Description of the Figures

The present invention will be described with reference to the accompanying drawings, wherein:

FIG. 1 is a diagram depicting the steps involved in the intrinsic and extrinsic blood clotting cascades, from time of trauma to the activation of factor X.

FIG. 2 is a diagram depicting the steps following initial intrinsic and extrinsic blood clotting cascades, beginning with the formation of Xa and culminating in the formation of a thrombus.

#### Detailed Description

Two blood coagulation pathways are associated with normal hemostasis: intrinsic and extrinsic. These two coagulation pathways converge in the formation of factor Xa. But, these two coagulation pathways are interdependent because complete elimination of the intrinsic pathway leads to uncontrolled bleeding. For example, Type B hemophiliacs completely lack factor IX or factor IX function and have a phenotype characterized by a severe bleeding disorder. Thus, the direct factor VIIa/tissue factor activation of factor X, which bypasses the need for factor VIII and factor IX, is insufficient for normal hemostasis. Conversely, formation of the factor VIIIa/IXa phospholipid factor X activator (tenase complex) (20) is essential for normal hemostasis.

Selective inhibition of the intrinsic pathway of coagulation with a factor IX antagonist can provide a method to inhibit the clotting cascade associated with some surgery, stroke, myocardial infarction and hemodialysis while leaving the clotting pathway associated with external lesions such as trauma or abscess intact. Factor IX is primarily associated with the intrinsic clotting pathway. A specific antagonist of factor IX should have a therapeutic benefit in diseases associated with intrinsic pathway clotting by inhibiting intravascular thrombosis. Also, a specific antagonist of factor IX should not have the side effect of unwanted or uncontrollable bleeding by impairing extravascular hemostasis associated with wound healing.

Some point mutations in factor IX partially inhibit its function and result in a mild or moderate phenotype manifested as a non-life threatening bleeding disorder [Bowen, D. J., J. Clin. Pathol: Mol. Pathol. 55:1-18 (2002)]. These point mutations cause factor IX to behave as if it were subject to a partial antagonist. In the presence of a partial antagonist, factor IX should maintain some activity, even at saturation levels of the partial antagonist. As a result of the point mutations in factor IX, its activity is reduced along with clotting associated with the intrinsic pathway, but some residual activity remains that leaves the extrinsic pathway intact.

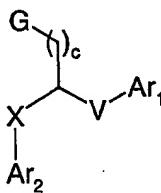
The present invention provides compositions and methods that inhibit the clotting activity of factor IX. Inhibition of hemostasis with agents that selectively inhibit the intrinsic pathway of factor X activation should leave the extrinsic pathway intact and allow the formation of small, but hemostatically important amounts of factor Xa and thrombin.

Embodiments of the present invention provide compounds of Formula (I) as depicted below. Embodiments of the present invention also provide methods of the preparation of compounds of Formula (I); pharmaceutical compositions comprising compounds of Formula (I); and methods for the use of compounds of Formula (I) and pharmaceutical compositions comprising compounds of Formula (I) in treating human or animal disorders. Compounds of the Formula (I) are useful as modulators of the intrinsic clotting pathway by inhibiting the biological activity of factor IX. Compounds of Formula (I) are useful in a variety of

applications including management, treatment, control, and/or as an adjunct of diseases in humans caused in part by the intrinsic clotting pathway utilizing factor IX. Such diseases or disease states include cardiopulmonary bypass, stroke, myocardial infarction, deep vein thrombosis associated with surgical procedures or long periods of confinement, acute and chronic inflammation and clotting associated with hemodialysis.

In a first aspect, the present invention provides a compound comprising at least one moiety of the formula I. Such compounds are useful in a variety of applications including for the management, treatment, control, and/or as an adjunct of diseases in humans caused in part by the intrinsic clotting pathway utilizing factor IX, will be discussed in more detail below.

10 In one aspect, the present invention provides compounds which are represented by  
Formula I:



(1)

15 wherein c is equal to 0, 1, or 2; wherein the values of 0, 1, and 2 comprise a direct bond, -CH<sub>2</sub>-, and -CH<sub>2</sub>-CH<sub>2</sub>-, optionally substituted 1 to 4 times with a substituent group, wherein said substituent group(s) or the term substituted refers to groups comprising: -alkyl, -aryl, -alkylene-aryl, -arylene-alkyl, -alkylene-arylene-alkyl, -O-alkyl, -O-aryl, or -hydroxyl. In preferred embodiments, c is equal to 0 or 1. In especially preferred embodiments, c is equal to 0.

G comprises: -hydrogen,  $-\text{CO}_2\text{R}_1$ ,  $-\text{CH}_2\text{OR}_1$ ,  $-\text{C}(\text{O})-\text{R}_1$ ,  $-\text{C}(\text{R}_1)=\text{N}-\text{O}-\text{R}_2$ , or an acid isostere; wherein  $\text{R}_1$  and  $\text{R}_2$  independently comprise: -hydrogen, -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, or -alkylene-arylene-alkyl. In preferred embodiments, G comprises: -hydrogen or  $-\text{CO}_2\text{R}_1$ ; wherein  $\text{R}_1$  comprises: -hydrogen, -alkyl, or -aryl. In especially preferred embodiments, G comprises: -hydrogen or  $-\text{CO}_2\text{H}$ .

30 V comprises:  $-(CH_2)_b-O-(CH_2)_a-$ ,  $-(CH_2)_b-N(R_7)-(CH_2)_a-$ ,  $-(CH_2)_b-O-$ ,  $-(CH_2)_b-N(R_7)-$ ,  $-(CH_2)_a-$ , or a direct bond; in which a is equal to 0, 1, or 2, b is equal to 1 or 2, and  $R_7$  comprises: -hydrogen, -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, or -alkylene-arylene-alkyl; wherein the values of 0, 1, and 2 comprise a direct bond,  $-CH_2-$ , and  $-CH_2-CH_2-$ , optionally

substituted 1 to 4 times with a substituent group, wherein said substituent group(s) or the term substituted refers to groups comprising: -alkyl, -aryl, -alkylene-aryl, -arylene-alkyl, -alkylene-arylene-alkyl, -O-alkyl, -O-aryl, or -hydroxyl. In preferred embodiments, V comprises:  $-(CH_2)_a-$ ,  $-(CH_2)_b-O-(CH_2)_a-$ , or a direct bond, wherein

5 a is equal to 1 or 2, and b is equal to 1. In especially preferred embodiments, V comprises:  $-(CH_2)_a-$  or a direct bond, wherein a is equal to 1.

X comprises:  $-N(R_8)-$ ,  $-CON(R_8)-$ ,  $-N(R_8)CO-$ ,  $-N(R_8)CON(R_9)-$ ,  $-OC(O)N(R_8)-$ ,  $-SO_2N(R_8)-$ , or  $-N(R_8)SO_2N(R_9)-$ ; wherein  $R_8$  and  $R_9$  independently comprise: -hydrogen,

10 -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, -alkylene-arylene-alkyl, -alkylene-cycloalkylene- $C(O)$ -alkylene-aryl, -alkylene-heterocyclylene- $C(O)$ -alkylene-aryl, -alkylene- $C(H)(R_{10})(R_{11})$ , or -alkylene- $N-(R_{10})(R_{11})$ ,

wherein  $R_{10}$  comprises H, alkyl, alkylene-aryl, alkylene-heteroaryl, aryl, or heteroaryl,

15 and  $R_{11}$  comprises H, -alkyl, -alkylene-aryl, -alkylene-heteroaryl, -aryl, -heteroaryl,  $-C(O)-O$ -alkyl,  $-C(O)-O$ -alkylene-aryl,  $-C(O)-O$ -alkylene-heteroaryl,  $-C(O)$ -alkyl,  $-C(O)$ -alkylene-aryl,  $-C(O)$ -alkylene-heteroaryl,  $-S(O)_2$ -alkyl,  $-S(O)_2$ -aryl,  $-S(O)_2$ -heteroaryl,  $-S(O)_2$ -alkylene-aryl,  $-S(O)_2$ -alkylene-heteroaryl,  $-S(O)_2$ -NH-alkyl,  $-S(O)_2$ -NH-alkylene-aryl,  $-S(O)_2$ -NH-alkylene-heteroaryl,  $-S(O)_2$ -NH-aryl, or  $-S(O)_2$ -NH-heteroaryl;

20  $R_{10}$  and  $R_{11}$  may be taken together to form a ring having the formula  $-(CH_2)_m-Z-(CH_2)_n-$  bonded to the nitrogen or carbon atom to which  $R_{10}$  and  $R_{11}$  are attached, wherein m and n are, independently, 1, 2, 3, or 4; Z independently comprises  $-CH_2-$ ,  $-C(O)-$ ,  $-O-$ ,  $-N(H)-$ ,  $-S-$ ,  $-S(O)-$ ,  $-S(O)_2-$ ,  $-CON(H)-$ ,  $-NHC(O)-$ ,  $-NHC(O)N(H)-$ ,  $-NH(SO_2)-$ ,  $-S(O)_2N(H)-$ ,  $-(O)CO-$ ,  $-NHS(O)_2NH-$ ,  $-OC(O)-$ ,  $-N(R_{12})-$ ,  $-N(C(O)R_{12})-$ ,  $-N(C(O)NHR_{12})-$ ,  $-N(S(O)_2NHR_{12})-$ ,  $-N(SO_2R_{12})-$ , or  $-N(C(O)OR_{12})-$ ; or

25

$R_{10}$  and  $R_{11}$  may be taken together, with the nitrogen or carbon atom to which they are attached, to form a heterocyclyl or heteroaryl ring.

30  $R_{12}$  comprises hydrogen, aryl, alkyl, or alkylene-aryl;

In preferred embodiments, X comprises:  $-N(R_8)-$ ,  $-CON(R_8)-$ ,  $-N(R_8)CO-$ , or  $-N(R_8)CON(R_9)-$ , wherein  $R_8$  and  $R_9$  independently comprise: -hydrogen, -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, or -alkylene-arylene-alkyl. In especially preferred embodiments, X comprises:

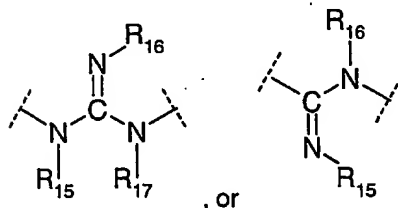
-N(R<sub>8</sub>)-, -CON(R<sub>8</sub>)-, or -N(R<sub>8</sub>)CO-, wherein R<sub>8</sub> comprises: -hydrogen, -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, or -alkylene-arylene-alkyl.

- Ar<sub>1</sub> comprises an aryl, heteroaryl, fused cycloalkylaryl, fused cycloalkylheteroaryl, fused heterocyclaryl, or fused heterocyclheteroaryl group optionally substituted 1 to 7 times. In preferred embodiments, Ar<sub>1</sub> comprises a mono- or bicyclic aryl or heteroaryl group optionally substituted 1 to 7 times. In especially preferred embodiments, Ar<sub>1</sub> comprises a phenyl group having 1 to 5 substituents, wherein the substituents independently comprise:
- a) -fluoro;
  - b) -chloro;
  - c) -bromo;
  - d) -iodo;
  - e) -cyano;
  - f) -nitro;
  - g) -perfluoroalkyl;
  - h) -D<sub>1</sub>-R<sub>13</sub>;
  - i) -alkyl;
  - j) -aryl;
  - k) -heteroaryl;
  - l) -heterocyclyl;
  - m) -cycloalkyl;
  - n) -alkylene-aryl;
  - o) -alkylene-heteroaryl;
  - p) -alkylene-arylene-D<sub>1</sub>-R<sub>13</sub>;
  - q) -alkylene-heteroarylene-D<sub>1</sub>-R<sub>13</sub>;
  - r) -alkylene-arylene-aryl;
  - s) -alkylene-heteroarylene-aryl;
  - t) -alkylene-arylene-heteroaryl;
  - u) -alkylene-arylene-arylene-D<sub>1</sub>-R<sub>13</sub>;
  - v) -alkylene-arylene-alkyl;
  - w) -alkylene-heteroarylene-alkyl;
  - x) -arylene-alkyl;
  - y) -arylene-cycloalkyl;
  - z) -heteroarylene-alkyl;
  - aa) -arylene-arylene-alkyl;
  - bb) -D<sub>1</sub>-alkyl;

- cc) - D<sub>1</sub>-aryl;
- dd) - D<sub>1</sub>-heteroaryl;
- ee) -D<sub>1</sub>-arylene-D<sub>2</sub>-R<sub>14</sub>;
- ff) -D<sub>1</sub>-heteroarylene-D<sub>2</sub>-R<sub>14</sub>;
- 5 gg) - D<sub>1</sub>-alkylene-heteroaryl;
- hh) - D<sub>1</sub>-alkylene-aryl;
- ii) -D<sub>1</sub>-alkylene-arylene-D<sub>2</sub>-R<sub>14</sub>
- jj) -D<sub>1</sub>-alkylene-heteroarylene-D<sub>2</sub>-R<sub>14</sub>
- kk) - D<sub>1</sub>-arylene-alkyl;
- 10 ll) - D<sub>1</sub>-heteroarylene-alkyl;
- mm) - D<sub>1</sub>-alkylene-arylene-aryl;
- nn) - D<sub>1</sub>-alkylene-heteroarylene-aryl;
- oo) - D<sub>1</sub>-arylene-arylene-aryl;
- pp) - D<sub>1</sub>-alkylene-arylene-alkyl;
- 15 qq) - D<sub>1</sub>-alkylene-heteroarylene-alky
- ss) -alkylene-D<sub>1</sub>-alkylene-aryl;
- tt) -alkylene-D<sub>1</sub>-alkylene-arylene-D<sub>2</sub>-R<sub>14</sub>
- uu) -arylene- D<sub>1</sub>-alkyl;
- vv) -arylene- D<sub>1</sub>-cycloalkyl;
- 20 ww) -arylene- D<sub>1</sub>-heterocyclyl;
- xx) -alkylene- D<sub>1</sub>-aryl;
- yy) -alkylene- D<sub>1</sub>-heteroaryl;
- zz) -alkylene-D<sub>1</sub>-arylene-D<sub>2</sub>-R<sub>14</sub>
- aaa) -alkylene-D<sub>1</sub>-heteroarylene-D<sub>2</sub>-R<sub>14</sub>
- 25 bbb) -alkylene- D<sub>1</sub>-heteroaryl;
- ccc) -alkylene- D<sub>1</sub>-cycloalkyl;
- ddd) -alkylene- D<sub>1</sub>-heterocyclyl;
- eee) -alkylene- D<sub>1</sub>-arylene-alkyl;
- fff) -alkylene- D<sub>1</sub>-heteroarylene-alkyl;
- 30 ggg) -alkylene- D<sub>1</sub>-alkylene-arylene-alkyl;
- hh) -alkylene- D<sub>1</sub>-alkylene-heteroarylene-alkyl;
- iii) -alkylene- D<sub>1</sub>-alkyl;
- jjj) -alkylene- D<sub>1</sub>-R<sub>13</sub>;
- kkk) -arylene- D<sub>1</sub>-R<sub>13</sub>;
- 35 ll) -heteroarylene-D<sub>1</sub>-R<sub>13</sub>; or
- mmm) -hydrogen;

wherein D<sub>1</sub> comprises -CH<sub>2</sub>-, -alkylene-, -alkenylene-, -alkylene-S-, -S-alkylene-, -alkylene-O-, -O-alkylene-, -alkylene-S(O)<sub>2</sub>-, -S(O)<sub>2</sub>-alkylene,

-O-, -N(R<sub>15</sub>)-, -C(O)-, -CON(R<sub>15</sub>)-, -N(R<sub>15</sub>)C(O)-, -N(R<sub>15</sub>)CON(R<sub>16</sub>)-, -N(R<sub>15</sub>)C(O)O-,  
 5 -OC(O)N(R<sub>15</sub>)-, -N(R<sub>15</sub>)SO<sub>2</sub>-, -SO<sub>2</sub>N(R<sub>15</sub>)-, -C(O)-O-, -O-C(O)-, -S-, -S(O)-, -S(O<sub>2</sub>)-,  
 -N(R<sub>15</sub>)SO<sub>2</sub>N(R<sub>16</sub>)-,



, and wherein R<sub>13</sub>, R<sub>15</sub>, R<sub>16</sub>, and R<sub>17</sub> independently comprise: -hydrogen, -alkyl, -aryl, -heteroaryl, -arylene-alkyl, -heteroarylene-alkyl, -alkylene-aryl, -alkylene-heteroaryl, -alkylene-arylene-alkyl, or -alkylene-heteroarylene-alkyl.

10

D<sub>2</sub> comprises -CH<sub>2</sub>-, -alkylene-, -alkenylene-, -alkylene-S-, -S-alkylene-, -alkylene-O-, -O-alkylene-, -alkylene-S(O)<sub>2</sub>-, -S(O)<sub>2</sub>-alkylene, -O-, -N(R<sub>25</sub>)-, -C(O)-, -CON(R<sub>25</sub>)-, -N(R<sub>18</sub>)C(O)-, -N(R<sub>18</sub>)CON(R<sub>19</sub>)-, -N(R<sub>18</sub>)C(O)O-, -OC(O)N(R<sub>18</sub>)-, -N(R<sub>18</sub>)SO<sub>2</sub>-, -SO<sub>2</sub>N(R<sub>18</sub>)-, -C(O)-O-,  
 15 -O-C(O)-, -S-, -S(O)-, -S(O<sub>2</sub>)-, -N(R<sub>18</sub>)SO<sub>2</sub>N(R<sub>19</sub>)-,  
 and wherein R<sub>18</sub> and R<sub>19</sub> independently comprise: -hydrogen, -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, or -alkylene-arylene-alkyl.

R<sub>14</sub> comprises -hydrogen, -alkyl, -aryl, -heteroaryl, -arylene-alkyl, -heteroarylene-alkyl, -alkylene-aryl, -alkylene-heteroaryl, -alkylene-arylene-alkyl, or -alkylene-heteroarylene-alkyl.

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The most preferred embodiments of Ar<sub>1</sub> are those in which Ar<sub>1</sub> comprises a mono-substituted phenyl group wherein the substituent comprises: -aryl, -arylene-alkyl, -D<sub>1</sub>-aryl, -D<sub>1</sub>-alkylene-arylene-alkyl, or -arylene-D<sub>1</sub>-alkyl; wherein D<sub>1</sub> comprises -O-, -N(R<sub>15</sub>)-, -CON(R<sub>15</sub>)-, or -N(R<sub>15</sub>)C(O)-, and wherein R<sub>15</sub> comprises: -hydrogen; -alkyl; or -aryl.

25

Ar<sub>2</sub> comprises an aryl or heteroaryl group optionally substituted 1 to 7 times. In preferred embodiments, Ar<sub>2</sub> comprises a phenyl, naphthyl, pyridyl, isoquinolyl, pyrimidyl or quinazolyl group optionally substituted 1 to 7 times. In especially preferred embodiments, Ar<sub>2</sub> comprises a substituted phenyl, 2-naphthyl, 2-pyridyl, 3-isoquinolyl, 2-pyrimidyl or 2-quinazolyl group having 1 to 5 substituents wherein the substituents independently comprise:

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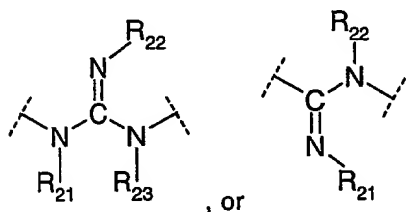
a) -fluoro;



- b) -chloro;  
c) -bromo;  
d) -iodo;  
e) -cyano;  
5 f) -nitro;  
g) -perfluoroalkyl;  
h) -T<sub>1</sub>-R<sub>20</sub>;  
i) -alkyl;  
j) -aryl;  
10 k) -heteroaryl;  
l) -heterocyclyl;  
m) -cycloalkyl;  
n) -alkylene-aryl;  
o) -alkylene-arylene-aryl;  
15 p) -alkylene-arylene-alkyl;  
q) -arylene-alkyl;  
r) -arylene-aryl;  
s) -arylene-heteroaryl;  
t) -heteroarylene-aryl;  
20 u) -heteroarylene-heteroaryl;  
v) -heteroarylene-heterocyclyl  
w) -arylene-heterocyclyl  
x) -arylene-arylene-alkyl;  
y) -T<sub>1</sub>-alkyl;  
25 z) -T<sub>1</sub>-aryl;  
aa) -T<sub>1</sub>-alkylene-aryl;  
bb) -T<sub>1</sub>-alkenylene-aryl;  
cc) -T<sub>1</sub>-alkylene-heteroaryl;  
dd) -T<sub>1</sub>-alkenylene-heteroaryl;  
30 ee) -T<sub>1</sub>-cycloalkylene-aryl;  
ff) -T<sub>1</sub>-cycloalkylene-heteroaryl;  
  
gg) -T<sub>1</sub>-heterocyclylene-aryl;  
35 hh) -T<sub>1</sub>-heterocyclylene-heteroaryl;  
ii) -T<sub>1</sub>-arylene-alkyl;  
jj) -T<sub>1</sub>-arylene-alkenyl;

- kk) - T<sub>1</sub>-alkylene-arylene-aryl;  
 ll) - T<sub>1</sub>-arylene-T<sub>2</sub>-aryl;  
 mm) - T<sub>1</sub>-arylene-arylene-aryl;  
 nn) - T<sub>1</sub>-alkylene-arylene-alkyl;  
 5 oo) -alkylene-T<sub>1</sub>-alkylene-aryl;  
 pp) -arylene-T<sub>1</sub>-alkyl;  
 qq) -arylene-T<sub>1</sub>-alkylene-aryl;  
 rr) -T<sub>1</sub>-alkylene-T<sub>2</sub>-aryl;  
 ss) -T<sub>1</sub>-alkylene-aryl;  
 10 tt) -alkylene-T<sub>1</sub>-heteroaryl;  
 uu) -alkylene-T<sub>1</sub>-cycloalkyl;  
 vv) -alkylene-T<sub>1</sub>-heterocyclyl;  
 ww) -alkylene-T-arylene-alkyl;  
 xx) -alkylene-T<sub>1</sub>-alkylene-arylene-alkyl;  
 15 yy) -alkylene-T<sub>1</sub>-alkyl;  
 zz) -alkylene-T<sub>1</sub>-R<sub>20</sub>;  
 aaa) -arylene- T<sub>1</sub>-R<sub>20</sub>; or  
 bbb) -hydrogen;

wherein T<sub>1</sub> comprises -CH<sub>2</sub>-, -O-, -N(R<sub>21</sub>)-, -C(O)-, -CON(R<sub>21</sub>)-, -N(R<sub>21</sub>)C(O)-,  
 20 -N(R<sub>21</sub>)CON(R<sub>22</sub>)-, -N(R<sub>21</sub>)C(O)O-, -OC(O)N(R<sub>21</sub>)-, -N(R<sub>21</sub>)SO<sub>2</sub>-, -SO<sub>2</sub>N(R<sub>21</sub>)-, -C(O)-O-,  
 -O-C(O)-, -S-, -S(O)-, -S(O<sub>2</sub>)-, -N(R<sub>21</sub>)SO<sub>2</sub>N(R<sub>22</sub>)-,



comprise: -hydrogen, -alkyl, -alkenyl, -alkylene-cycloalkyl, -alkynene-heterocyclyl, -aryl, -  
 heteroaryl, -arylene-alkyl, -alkylene-aryl, -alkylene-arylene-alkyl, -alkylene-arylene-aryl, -  
 25 alkylene-arylene-alkylene-aryl, -alkylene-arylene-O-arylene, or alkylene-arylene-O-alkylene-  
 aryl; and

wherein T<sub>2</sub> comprises a direct bond, -CH<sub>2</sub>-, -O-, -N(R<sub>24</sub>)-, -C(O)-, -CON(R<sub>24</sub>)-, -N(R<sub>24</sub>)C(O)-,  
 -N(R<sub>24</sub>)CON(R<sub>25</sub>)-, -N(R<sub>24</sub>)C(O)O-, -OC(O)N(R<sub>24</sub>)-, -N(R<sub>24</sub>)SO<sub>2</sub>-, -SO<sub>2</sub>N(R<sub>24</sub>)-, -C(O)-O-,  
 30 -O-C(O)-, -S-, -S(O)-, -S(O<sub>2</sub>)-, -N(R<sub>24</sub>)SO<sub>2</sub>N(R<sub>25</sub>)-, wherein R<sub>24</sub> and R<sub>25</sub> independently  
 comprise: -hydrogen, -alkyl, -alkenyl, -alkylene-cycloalkyl, -alkynene-heterocyclyl, -aryl, -  
 heteroaryl, -arylene-alkyl, -alkylene-aryl, and -alkylene-arylene-alkyl.

The most preferred embodiments of Ar<sub>2</sub> are those in which Ar<sub>2</sub> comprises a substituted phenyl, 2-naphthyl, 2-pyridyl, 3-isoquinolyl, 2-pyrimidyl or 2-quinazolyl group having 1 to 5 substituents independently comprising:

- 5 a) -fluoro;
- b) -chloro;
- c) -bromo;
- d) -iodo;
- e) -cyano;
- 10 f) -nitro;
- g) -perfluoroalkyl;
- h) -T<sub>1</sub>-R<sub>20</sub>;
- i) -alkyl;
- j) -aryl;
- 15 k) -arylene-alkyl;
- l) -T<sub>1</sub>-alkyl;
- m) -T<sub>1</sub>-alkylene-aryl;
- n) -T<sub>1</sub>-alkylene-arylene-aryl;
- o) -T<sub>1</sub>-alkylene-arylene-alkyl;
- 20 p) -arylene-T<sub>1</sub>-alkyl; or
- q) -hydrogen;

wherein T<sub>1</sub> comprises -CH<sub>2</sub>-, -O-, -N(R<sub>21</sub>)-, -CON(R<sub>21</sub>)-, or -N(R<sub>21</sub>)C(O)-; wherein R<sub>20</sub> and R<sub>21</sub> independently comprise: -hydrogen, -alkyl, or -aryl.

25 The alkyl, aryl, heteroaryl, alkylene, and arylene groups in Ar<sub>1</sub>, Ar<sub>2</sub>, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub>, R<sub>11</sub>, R<sub>12</sub>, R<sub>13</sub>, R<sub>14</sub>, R<sub>15</sub>, R<sub>16</sub>, R<sub>17</sub>, R<sub>18</sub>, R<sub>19</sub>, R<sub>20</sub>, R<sub>21</sub>, R<sub>22</sub>, and R<sub>23</sub> may be optionally substituted 1 to 4 times with a substituent group, wherein said substituent group(s) or the term substituted refers to groups comprising:

- a) -hydrogen;
- 30 b) -fluoro;
- c) -chloro;
- d) -bromo;
- e) -iodo;
- f) -cyano;
- 35 g) -nitro;
- h) -perfluoroalkyl;
- i) -Q-perfluoroalkyl

- j) -Q-R<sub>24</sub>;
- k) -Q-alkyl;
- l) -Q-aryl;
- m) -Q-alkylene-aryl;
- 5 n) -Q-alkylene-NR<sub>25</sub>R<sub>26</sub>; or
- o) -Q-alkyl-W-R<sub>27</sub>;

wherein Q and W independently comprise: -CH<sub>2</sub>-, -O-, -N(R<sub>28</sub>)-, -C(O)-, -CON(R<sub>28</sub>)-,  
 -N(R<sub>28</sub>)C(O)-, -N(R<sub>28</sub>)CON(R<sub>29</sub>)-, -N(R<sub>28</sub>)C(O)O-, -OC(O)N(R<sub>28</sub>)-, -N(R<sub>28</sub>)SO<sub>2</sub>-, -SO<sub>2</sub>N(R<sub>28</sub>)-, -  
 C(O)-O-, -O-C(O)-, or -N(R<sub>28</sub>)SO<sub>2</sub>N(R<sub>29</sub>)-, wherein R<sub>24</sub>, R<sub>25</sub>, R<sub>26</sub>, R<sub>27</sub>, R<sub>28</sub>, and R<sub>29</sub>  
 10 independently comprise: -hydrogen, -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, or -alkylene-  
 arylene-alkyl.

Also included within the scope of the invention are the individual enantiomers of the  
 compounds represented by Formula (I) above as well as any wholly or partially racemic  
 15 mixtures thereof. The present invention also covers the individual enantiomers of the  
 compounds represented by formula above as mixtures with diastereoisomers thereof in  
 which one or more stereocenters are inverted.

In one group of particularly preferred embodiments, the compounds are represented  
 20 by Formula (I), in which c is equal to 0; G comprises: -hydrogen or -CO<sub>2</sub>H; V comprises: -  
 CH<sub>2</sub>- or a direct bond; X comprises: -CON(R<sub>8</sub>)-, or -N(R<sub>8</sub>)CO- wherein R<sub>8</sub> comprises: -  
 hydrogen; Ar<sub>1</sub> comprises a mono-substituted phenyl group wherein the substituent  
 comprises: -aryl, -arylene-alkyl, -D<sub>1</sub>-aryl -D<sub>1</sub>-alkylene-arylene-alkyl, or -arylene-D<sub>1</sub>-alkyl,  
 wherein D<sub>1</sub> comprises -O-, or -N(R<sub>15</sub>)-, wherein R<sub>15</sub> comprises: -hydrogen, -alkyl, or -aryl;  
 25 and Ar<sub>2</sub> comprises a substituted phenyl, 2-naphthyl, 2-pyridyl, 3-isoquinolyl, 2-pyrimidyl or 2-  
 quinazolyl group having 1 to 5 substituents independently comprising: -hydrogen, -fluoro, -  
 chloro, -bromo, iodo, -cyano, -nitro, -perfluoroalkyl, -T<sub>1</sub>-R<sub>14</sub>, -alkyl, -aryl, -arylene-alkyl, -T<sub>1</sub>-  
 alkyl, -T<sub>1</sub>-alkylene-aryl, -T<sub>1</sub>-alkylene-arylene-aryl, -T<sub>1</sub>-alkylene-arylene-alkyl, or -arylene-T<sub>1</sub>-  
 alkyl; wherein T<sub>1</sub> comprises -CH<sub>2</sub>-, -O-, -N(R<sub>21</sub>)-, -CON(R<sub>21</sub>)-, or -N(R<sub>21</sub>)C(O)-; wherein R<sub>21</sub>  
 30 comprises: -hydrogen, -alkyl, or -aryl. The alkyl, aryl, alkylene, and arylene groups in Ar<sub>1</sub>,  
 and Ar<sub>2</sub> may be optionally substituted 1 to 4 times with a substituent group, wherein said  
 substituent group(s) or the term substituted refers to groups comprising: -hydrogen, -fluoro, -  
 chloro, -bromo, iodo, -cyano, -nitro, or -perfluoroalkyl.

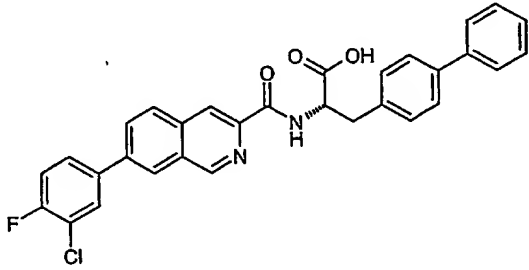
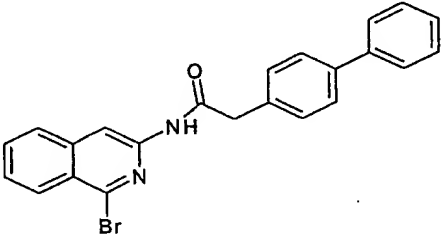
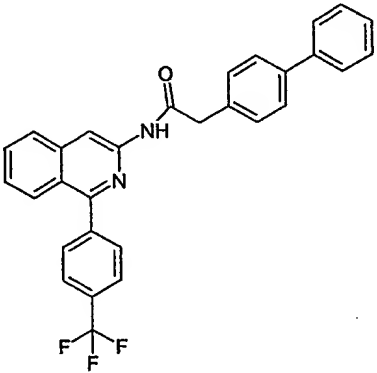
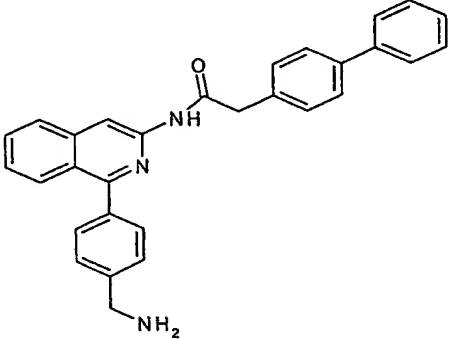
35 Compounds of the present invention having biological activity are listed below in  
 Table 1.

Unless indicated otherwise, the structures of Examples of compounds of Formula (I) in Table 1 and elsewhere having vacant connectivity for heteroatoms, such as oxygen and nitrogen, are assumed to have a hydrogen atom attached thereto.

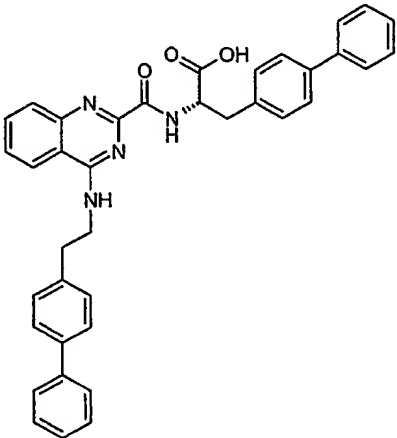
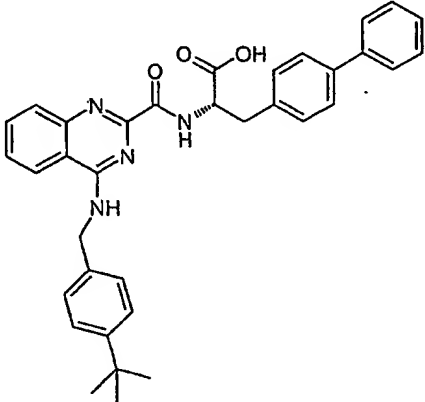
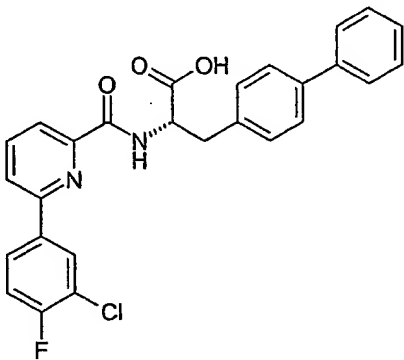
Table 1.

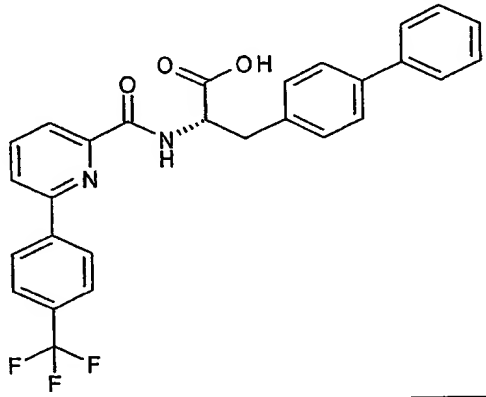
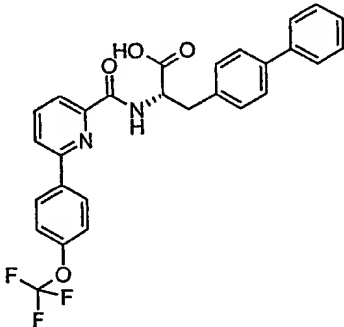
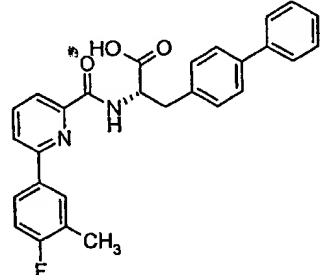
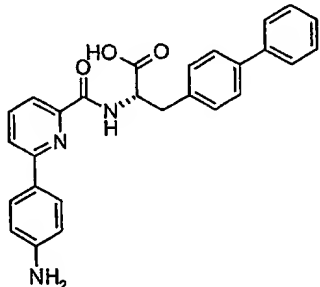
Example	Structure	Name
1		3-Biphenyl-4-yl-(2S)-[(isoquinoline-3-carbonyl)-amino]-propionic acid
2		(2S)-[(isoquinoline-3-carbonyl)-amino]-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid
3		(2S)-[(isoquinoline-3-carbonyl)-amino]-3-(3,5'-bistrifluoromethyl-biphenyl-4-yl)-propionic acid
4		(2S)-[(isoquinoline-3-carbonyl)-amino]-3-(4'-methoxy-biphenyl-4-yl)-propionic acid
5		3-[4-(4'-Cyano-phenoxy)-phenyl]-(2S)-[(isoquinoline-3-carbonyl)-amino]-propionic acid
6		3-[4-(4'-Nitro-phenoxy)-phenyl]-(2S)-[(isoquinoline-3-carbonyl)-amino]-propionic acid
7		3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-(2S)-[(isoquinoline-3-carbonyl)-amino]-propionic acid

Example	Structure	Name
8		3-(4'-Cyano-biphenyl-4-yl)- (2S)-[(isoquinoline-3- carbonyl)-amino]-propionic acid
9		(2S)-[(isoquinoline-3- carbonyl)-amino] -3-(3'-trifluoromethyl- biphenyl-4-yl)-propionic acid
10		(2S)-[(isoquinoline-3- carbonyl)-amino] -3-(3'-nitro-biphenyl-4-yl)- propionic acid
11		3-Biphenyl-4-yl-(2S)-[(7- bromo-isoquinoline-3- carbonyl)-amino]-propionic acid
12		3-Biphenyl-4-yl-(2S)-[(7-(4- trifluoromethyl-phenyl)- isoquinoline-3-carbonyl)- amino]-propionic acid

Example	Structure	Name
13		3-Biphenyl-4-yl-(2S)-[7-(3-chloro-4-fluoro-phenyl)-isoquinoline-3-carbonyl]-amino)-propionic acid
14		2-Biphenyl-4-yl-N-(1-bromo-isoquinolin-3-yl)-acetamide
15		2-Biphenyl-4-yl-N-[1(4-trifluoromethyl-phenyl)-isoquinolin-3-yl]-acetamide
16		N-[1(4-aminomethyl-phenyl)-isoquinolin-3-yl]-2-biphenyl-4-yl-acetamide

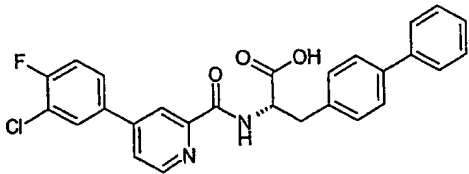
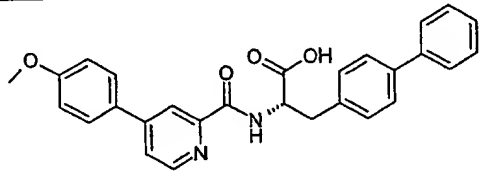
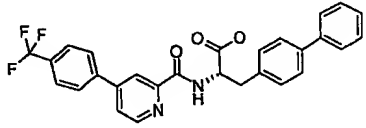
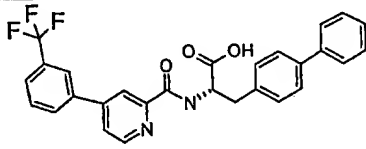
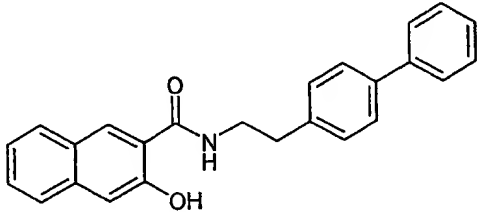
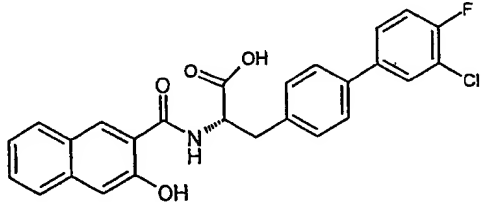


Example	Structure	Name
17		3-Biphenyl-4-yl-(2S)-[4-(2-biphenyl-4-yl-ethylamino)-quinazoline-2-carbonyl]-amino}- propionic acid
18		3-Biphenyl-4-yl-(2S)-[4- <i>tert</i> -butyl-benzylamino)-quinazoline-2-carbonyl]-amino}- propionic acid
19		3-Biphenyl-4-yl-(2S)-[6-(3-chloro-4-fluoro-phenyl)-pyridine-2-carbonyl]-amino}- propionic acid

Example	Structure	Name
20		3-Biphenyl-4-yl-(2S)-{[6-(3-chloro-4-fluoro-phenyl)-pyridine-2-carbonyl]-amino}-propionic acid
21		3-Biphenyl-4-yl-(2S)-{[6-(4-trifluoromethoxy-phenyl)-pyridine-2-carbonyl]-amino}-propionic acid
22		3-Biphenyl-4-yl-(2S)-{[6-(4-fluoro-3-methyl-phenyl)-pyridine-2-carbonyl]-amino}-propionic acid
23		(2S)-{[6-(4-Amino-phenyl)-pyridine-2-carbonyl]-amino}-3-biphenyl-4-yl-propionic acid

Example	Structure	Name
24		3-Biphenyl-4-yl-(2S)-{[6-(3-cyano-phenyl)-pyridine-2-carbonyl]-amino}-propionic acid
25		3-Biphenyl-4-yl-(2S)-{[6-(4-methanesulfonyl-phenyl)-pyridine-2-carbonyl]-amino}-propionic acid
26		3-Biphenyl-4-yl-(2S)-{[6-(4-methoxy-phenyl)-pyridine-2-carbonyl]-amino}-propionic acid
27		3-Biphenyl-4-yl-(2S)-{[6-(3-carboxamidino-phenyl)-pyridine-2-carbonyl]-amino}-propionic acid

Example	Structure	Name
28		3-Biphenyl-4-yl-(2S)-{[6-(4-phenoxy-phenyl)-pyridine-2-carbonyl]-amino}-propionic acid
29		3-Biphenyl-4-yl-(2S)-{[6-(4-tert-butyl-phenyl)-pyridine-2-carbonyl]-amino}-propionic acid
30		3-Biphenyl-4-yl-(2S)-{[5-(3-chloro-4-fluoro-phenyl)-pyridine-2-carbonyl]-amino}-propionic acid
31		3-Biphenyl-4-yl-(2S)-{[5-(4-trifluoromethyl-phenyl)-pyridine-2-carbonyl]-amino}-propionic acid
32		3-Biphenyl-4-yl-(2S)-{[5-(4-methoxy-phenyl)-pyridine-2-carbonyl]-amino}-propionic acid

Example	Structure	Name
33		3-Biphenyl-4-yl-(2S)-{[4-(3-chloro-4-fluoro-phenyl)-pyridine-2-carbonyl]-amino}-propionic acid
34		3-Biphenyl-4-yl-(2S)-{[4-(4-methoxy-phenyl)-pyridine-2-carbonyl]-amino}-propionic acid
35		3-Biphenyl-4-yl-(2S)-{[4-(4-trifluoromethyl-phenyl)-pyridine-2-carbonyl]-amino}-propionic acid
36		3-Biphenyl-4-yl-(2S)-{[4-(3-trifluoromethyl-phenyl)-pyridine-2-carbonyl]-amino}-propionic acid
37		3-Hydroxy-naphthalene-2-carboxylic acid (2-biphenyl-4-yl-ethyl)-amide
38		3-[(3'-Chloro-4'-fluoro)-biphenyl-4-yl]-(2S)-{[3-hydroxy-naphthalene-2-carbonyl]-amino}-propionic acid

Example	Structure	Name
39		3-(Biphenyl-4-yl)-(2S)-[(3-hydroxy-napthalene-2-carbonyl)-amino]-propionic acid
40		(2S)-[(3-Hydroxy-napthalene-2-carbonyl)-amino]-3-[(3'-nitro)-biphenyl-4-yl]-propionic acid
41		3-(Biphenyl-4-yl)-(2S)-[(3'-chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
42		3-(Biphenyl-4-yl)-(2S)-[(4'-trifluoromethyl-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
43		(2S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester
44		3-(4'-Nitro-biphenyl-4-yl)-(2S)-[(4'-trifluoromethyl-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester

Example	Structure	Name
45		3-(3'-Trifluoromethyl-biphenyl-4-yl)-(2S)-[(4'-trifluoromethyl-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
46		3-(4'-Trifluoromethyl-biphenyl-4-yl)-(2S)-[(4'-trifluoromethyl-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
47		3-Biphenyl-4-yl-(2S)-[(2',4'-difluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid
48		3-Biphenyl-4-yl-(2S)-[(4'-chloro-3'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
49		3-Biphenyl-4-yl-(2S)-[(3'-chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid
50		3-Biphenyl-4-yl-(2S)-[(4-hydroxy-3'-nitro-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
51		3-Biphenyl-4-yl-(2S)-[(4-hydroxy-4'-trifluoromethoxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester

Example	Structure	Name
52		(2S)-[(4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(3'-nitro-biphenyl-4-yl)-propionic acid
53		(2S)-[(4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(3'-nitro-biphenyl-4-yl)-propionic acid methyl ester
54		(2S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-nitro-biphenyl-4-yl)-propionic acid methyl ester
55		3-Biphenyl-4-yl-(2S)-[(4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
56		3-Biphenyl-4-yl-(2S)-[(4'-hydroxy-4'-methoxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
57		3-Biphenyl-4-yl-(2S)-[(4'-tert-butyl-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
58		(2S)-[(4-Hydroxy-3'-nitro-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester



Example	Structure	Name
59		3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-(2S)-[(4-hydroxy-3'-nitro-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
60		(2S)-[(4'-Amino-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-biphenyl-4-yl-propionic acid methyl ester
61		(2S)-[(3'-Amino-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-biphenyl-4-yl-propionic acid methyl ester
62		3-Biphenyl-4-yl-(2S)-[(5'-fluoro-4-hydroxy-2'-methoxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
63		3-Biphenyl-4-yl-(2S)-[(3'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
64		3-Biphenyl-4-yl-(2S)-[(4-hydroxy-3'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
65		3-Biphenyl-4-yl-(2S)-[(4-hydroxy-3',5'-bis-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
66		3-Biphenyl-4-yl-(2S)-[(3'-chloro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester

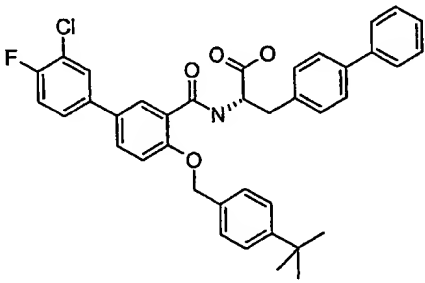
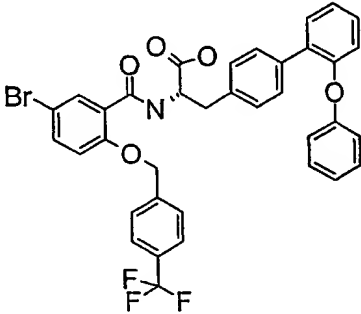
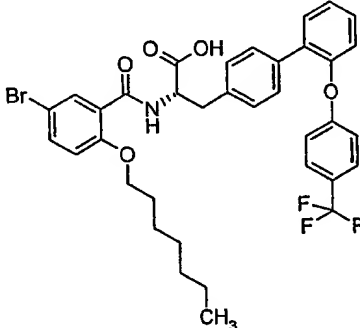
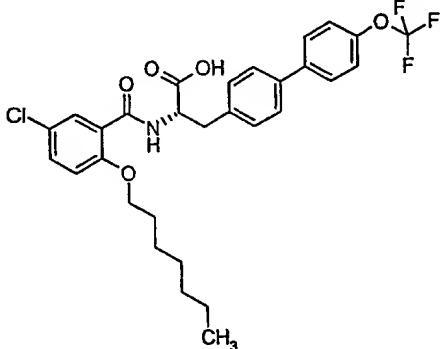
Example	Structure	Name
67		3-Biphenyl-4-yl-(2S)-[(4'-chloro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
68		3-Biphenyl-4-yl-(2S)-[(3',5'-difluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
69		3-Biphenyl-4-yl-(2S)-[(4'-fluoro-4-hydroxy-3'-methyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
70		(2S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester
71		(2S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(4'-methoxy-biphenyl-4-yl)-propionic acid methyl ester
72		3-Biphenyl-4-yl-(2S)-[(4-hydroxy-4'-trifluoromethoxy-biphenyl-3-carbonyl)-amino]-propionic acid
73		3-Biphenyl-4-yl-(2S)-[(4'-tert-butyl-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid

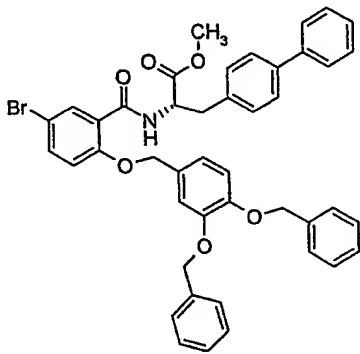
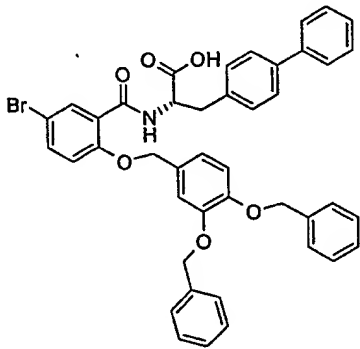
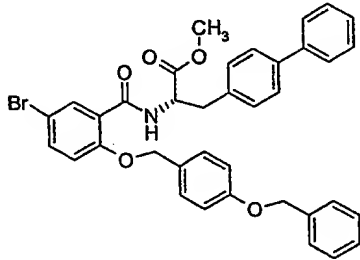
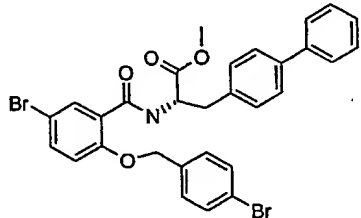
Example	Structure	Name
74		3-Biphenyl-4-yl-(2S)-[(4-hydroxy-3',4'-dimethoxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
75		(2S)-(5-Benzo[1,3]dioxol-5-yl-2-hydroxy-benzoylamino)-3-biphenyl-4-yl-propionic acid methyl ester
76		3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-(2S)-[(4-hydroxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
77		3-Biphenyl-4-yl-(2S)-[(4-hydroxy-4'-methanesulfonyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
78		(2S)-[(3'-Amino-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester
79		3-(3',5'-Bis-trifluoromethyl-biphenyl-4-yl)-(2S)-[(3'-chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
80		3-(3',5'-Bis-trifluoromethyl-biphenyl-4-yl)-(2S)-[(4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester

Example	Structure	Name
81		3-(3',5'-Bis-trifluoromethyl-biphenyl-4-yl)-(2S)-[(4-hydroxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
82		(2S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionic acid
83		(2S)-[(4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethoxy-biphenyl-4-yl)-propionic acid methyl ester
84		(2S)-[(4-Hydroxy-3'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester
85		4'-[(2S)-[(4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-2-methoxycarbonyl-ethyl]-5-nitro-biphenyl-3-carboxylic acid methyl ester
86		(2S)-[(4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(3',4',5'-trimethoxy-biphenyl-4-yl)-propionic acid methyl ester

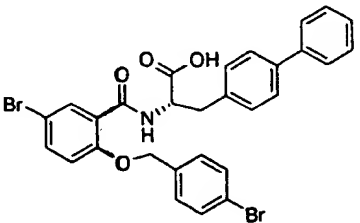
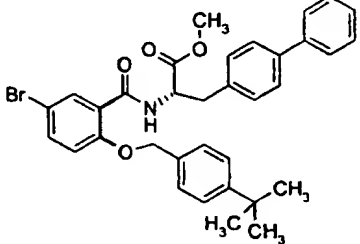
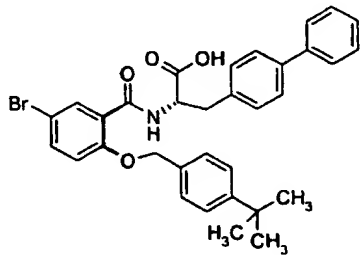
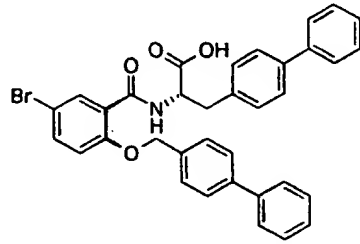
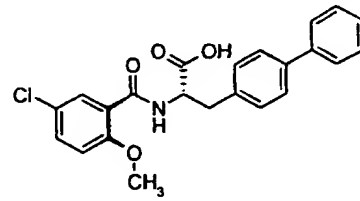
Example	Structure	Name
87		(2S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethoxy-biphenyl-4-yl)-propionic acid methyl ester
88		3-Biphenyl-4-yl-(2S)-[(4-hydroxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid
89		(2S)-[(4-Hydroxy-2'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(2'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester
90		3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-(2S)-[(3'-chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
91		(2S)-[(4-Hydroxy-3'-nitro-biphenyl-3-carbonyl)-amino]-3-(3'-nitro-biphenyl-4-yl)-propionic acid methyl ester
92		(2S)-[(4-Hydroxy-3'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(3'-nitro-biphenyl-4-yl)-propionic acid methyl ester

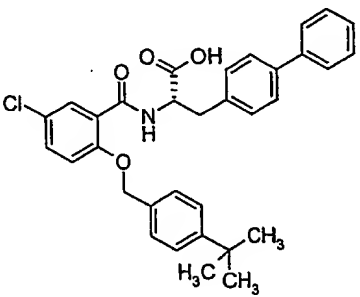
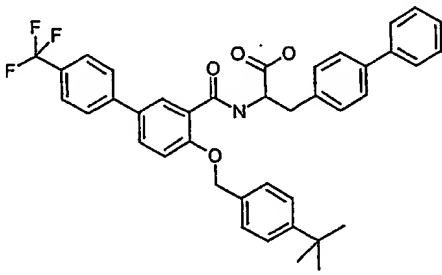
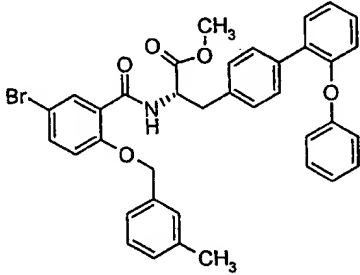
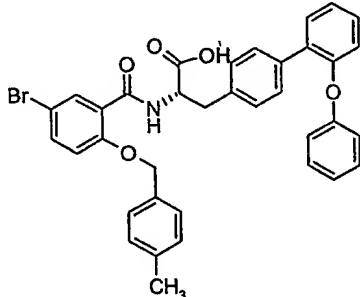
Example	Structure	Name
93		(2S)-[(4-Hydroxy-3'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester
94		3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-(2S)-[(4-hydroxy-3'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
95		3-Biphenyl-4-yl-(2S)-[(4-hydroxy-2'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
96		3-(3',5'-Bis-trifluoromethyl-biphenyl-4-yl)-(2S)-[(4-hydroxy-3'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester
97		(2S)-[(4-Hydroxy-3'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(2'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester
98		(2S)-[2-(4-Benzyloxy-benzyloxy)-5-bromo-benzoylamino]-3-biphenyl-4-yl-propionic acid

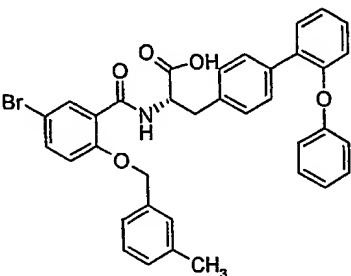
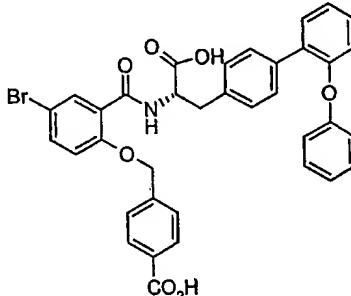
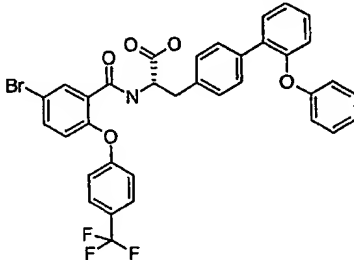
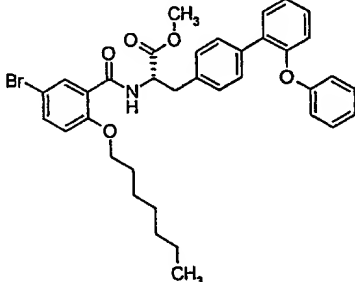
Example	Structure	Name
99		3-Biphenyl-4-yl-2S-[[4-(4-tert-butyl-benzyloxy)-3'-chloro-4'-fluoro-biphenyl-3-carbonyl]-amino]-propionic acid
100		(2S)-[5-Bromo-2-(4-trifluoromethyl-benzyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
101		(2S)-(5-Bromo-2-heptyloxy-benzoylamino)-3-[2'-(4-trifluoromethyl-phenoxy)-biphenyl-4-yl]-propionic acid
102		(2S)-(5-Chloro-2-heptyloxy-benzoylamino)-3-(4'-trifluoromethoxy-biphenyl-4-yl)-propionic acid

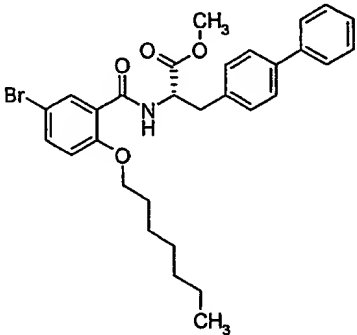
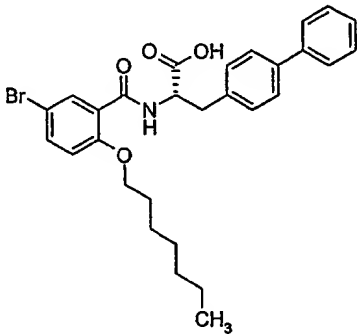
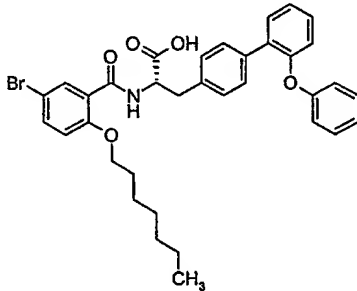
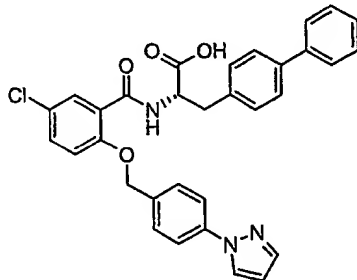
Example	Structure	Name
103		3-Biphenyl-4-yl-(2S)-[2-(3,4-bis-benzyloxy-benzyloxy)-5-bromo-benzoylamino] - propionic acid methyl ester
104		3-Biphenyl-4-yl-(2S)-[2-(3,4-bis-benzyloxy-benzyloxy)-5-bromo-benzoylamino]- propionic acid
105		(2S)-[2-(4-Benzyloxybenzyl oxy)-5-bromo-benzoylamino] -3-biphenyl-4-yl-propionic acid methyl ester
106		3-Biphenyl-4-yl-(2S)-[5-bromo-2-(4-bromo-benzyloxy)-benzoylamino]- propionic acid methyl ester



Example	Structure	Name
107		3-Biphenyl-4-yl-(2S)-[5-bromo-2-(4-bromobenzyloxy)-benzoylamino]-propionic acid
108		3-Biphenyl-4-yl-(2S)-[5-bromo-2-(4-tert-butylbenzyloxy)-benzoylamino]-propionic acid methyl ester
109		3-Biphenyl-4-yl-(2S)-[5-bromo-2-(4-tert-butylbenzyloxy)-benzoylamino]-propionic acid
110		3-Biphenyl-4-yl-(2S)-[2-(biphenyl-4-ylmethoxy)-5-bromo-benzoylamino]-propionic acid
111		3-Biphenyl-4-yl-(2S)-(5-chloro-2-methoxy-benzoylamino)-propionic acid

Example	Structure	Name
112		3-Biphenyl-4-yl-(2S)-[2-(4-tert-butyl-benzyloxy)-5-chloro-benzoylamino]-propionic acid
113		3-Biphenyl-4-yl-(2S)-[2-(4-tert-butyl-benzyloxy)-5-(4-trifluoromethylphenyl)-benzoylamino]-propionic acid
114		(2S)-[5-Bromo-2-(3-methyl-benzyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
115		(2S)-[5-Bromo-2-(4-methyl-benzyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

Example	Structure	Name
116		(2S)-[5-Bromo-2-(3-methylbenzyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
117		(2S)-[5-Bromo-2-(4-carboxybenzyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
118		(2S)-[5-Bromo-2-(4-trifluoromethyl-phenoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
119		(2S)-[5-Bromo-2-heptyloxy-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester

Example	Structure	Name
120		3-Biphenyl-4-yl-(2S)-(5-bromo-2-heptyloxy-benzoylamino)-propionic acid methyl ester
121		3-Biphenyl-4-yl-(2S)-(5-bromo-2-heptyloxy-benzoylamino)-propionic acid
122		(2S)-(5-Bromo-2-heptyloxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
123		3-Biphenyl-4-yl-(2S)-[5-chloro-2-(4-pyrazol-1-yl-benzyloxy)-benzoylamino]-propionic acid

Example	Structure	Name
124		(2S)-[5-Bromo-2-(4-tert-butyl-benzyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
125		(2S)-(2-Benzyloxy-5-bromo-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
126		(2S)-(2-Benzyloxy-5-bromo-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
127		(2S)-[5-Bromo-2-(4-bromo-benzyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
128		(2S)-(5-Bromo-2-propoxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
129		(2S)-[[5-Bromo-2,3-dihydro-benzofuran-7-carbonyl)-amino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

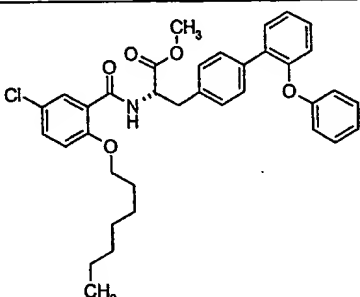
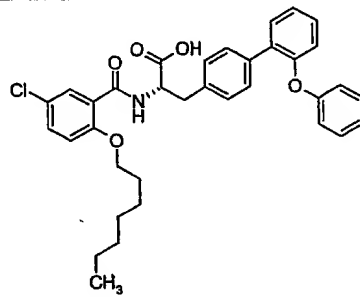
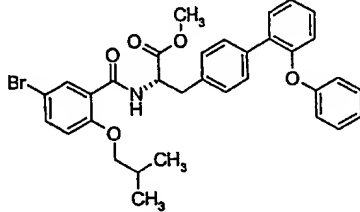
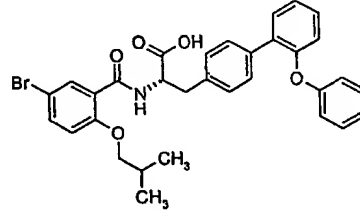
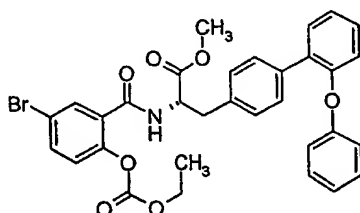
Example	Structure	Name
130		(2S)-[5-Bromo-2-(3-phenylallyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
131		(2S)-[5-Bromo-2-(3-phenylallyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
132		(2S)-[5-Bromo-2-(4-methanesulfonyl-benzyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
133		(2S)-[5-Bromo-2-(4-methanesulfonyl-benzyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
134		(2S)-[5-Bromo-2-(3-methylbutoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester

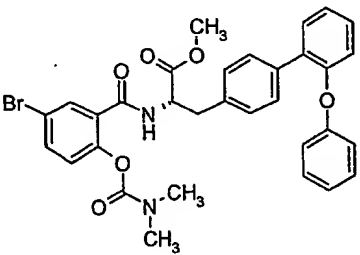
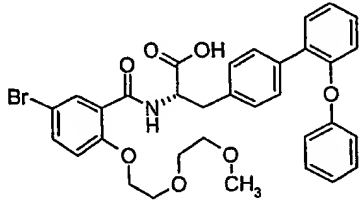
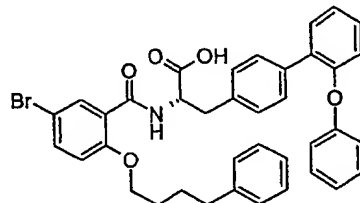
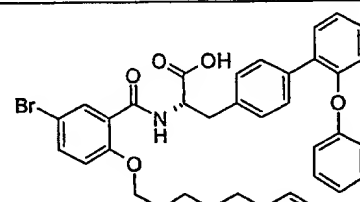
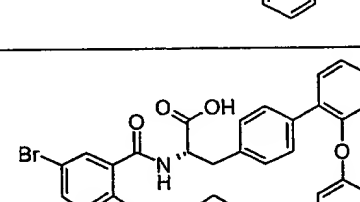
Example	Structure	Name
135		(2S)-[5-Bromo-2-(3-methylbutoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
136		(2S)-[2-(Biphenyl-4-ylmethoxy)-5-bromo-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
137		(2S)-[2-(Biphenyl-4-ylmethoxy)-5-bromo-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
138		(2S)-[5-Bromo-2-(4-methoxyphenoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
139		(2S)-[5-Bromo-2-(4-phenoxybenzyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

Example	Structure	Name
140		(2S)-[5-Bromo-2-(1-methylbutoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
141		(2S)-[5-Bromo-2-(1-methylbutoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
142		(2S)-[5-Bromo-2-isopropoxy-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
143		(2S)-[5-Bromo-2-(3-trifluoromethyl-phenoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
144		(2S)-[5-Bromo-2-heptyloxy-benzoylamino]-3-[2'-(4-methoxy-phenoxy)-biphenyl-4-yl]-propionic acid
145		(2S)-[5-Bromo-2-(2-morpholin-4-yl-ethoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester



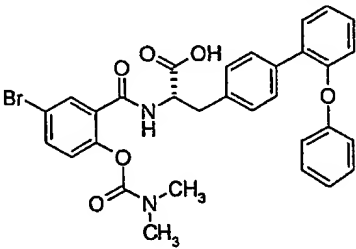
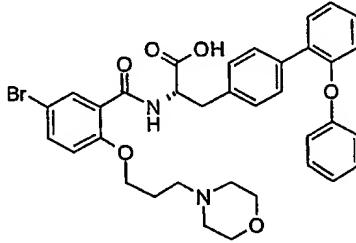
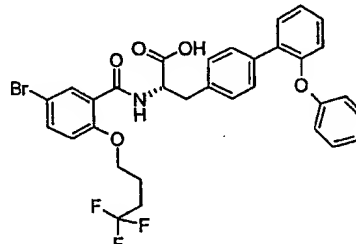
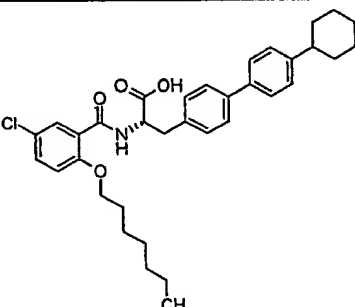
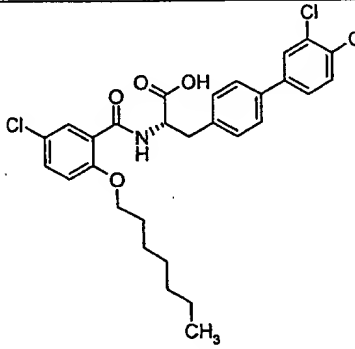
Example	Structure	Name
146		(2S)-{5-Bromo-2-[2-(2-methoxy-ethoxy)-ethoxy]-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
147		(2S)-{5-Bromo-2-[2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy]-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
148		(2S)-{5-Bromo-2-[2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy]-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
149		(2S)-{5-Bromo-2-[2-(2-oxo-pyrrolidin-1-yl)-ethoxy]-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
150		(2S)-[5-Bromo-2-(2-phenyl-cyclopropylmethoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
151		(2S)-{5-Bromo-2-sec-butoxy-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

Example	Structure	Name
152		(2S)-(5-Chloro-2-heptyloxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
153		(2S)-(5-Chloro-2-heptyloxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
154		(2S)-(5-Bromo-2-isobutoxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
155		(2S)-(5-Bromo-2-isobutoxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
156		(2S)-(5-Bromo-2-ethoxycarbonyloxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester

Example	Structure	Name
157		(2S)-(5-Bromo-2-dimethylcarbamoyloxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
158		(2S)-[5-Bromo-2-[2-(2-methoxy-ethoxy)-ethoxy]-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
159		(2S)[5-Bromo-2-(4-phenyl-butoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
160		(2S)-[5-Bromo-2-(5-phenyl-pentyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
161		(2S)-[5-Bromo-2-(6-phenyl-hexyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

Example	Structure	Name
162		(2S)-(5-Bromo-2-heptyloxy-benzoylamino)-3-[2'-(4-trifluoromethoxy-phenoxy)-biphenyl-4-yl]-propionic acid
163		(2S)-(5-Bromo-2-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
164		(2S)-[5-Bromo-2-(2-piperidin-1-yl-ethoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
165		(2S)-(5-Bromo-2-heptyloxy-benzoylamino)-3-[2'-(4-tert-butyl-phenoxy)-biphenyl-4-yl]-propionic acid
166		(2S)-(5-Chloro-2-heptyloxy-benzoylamino)-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid

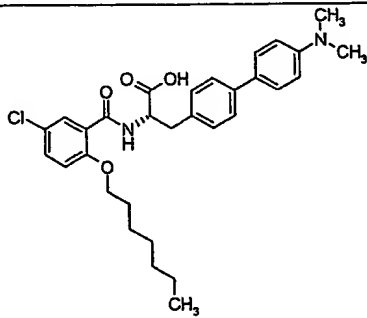
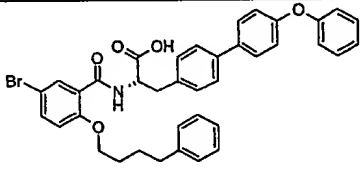
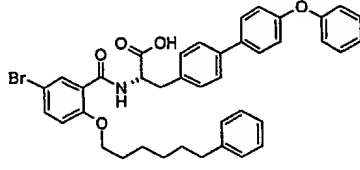
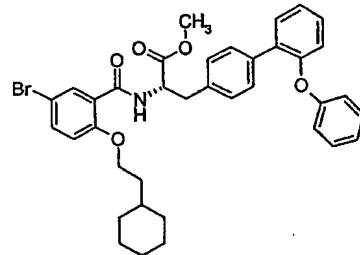
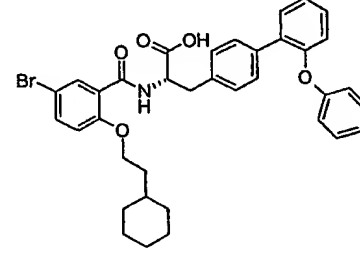
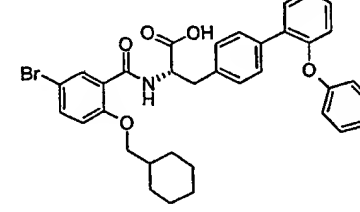
Example	Structure	Name
167		3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-(2S)-(5-chloro-2-heptyloxy-benzoylamino)-propionic acid
168		(2S)-[5-Bromo-2-(3-phenyl-propoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
169		(2S)-[5-Bromo-2-[3-(3,4-dimethoxy-phenyl)-propoxy]-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
170		(2S)-[5-Bromo-2-(3-pyridin-3-yl-propoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
171		(2S)-[5-Bromo-2-(3-pyridin-4-yl-propoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

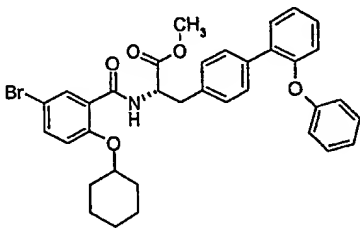
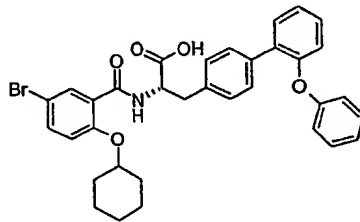
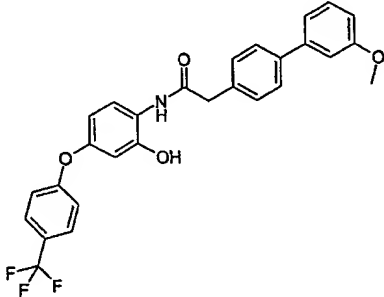
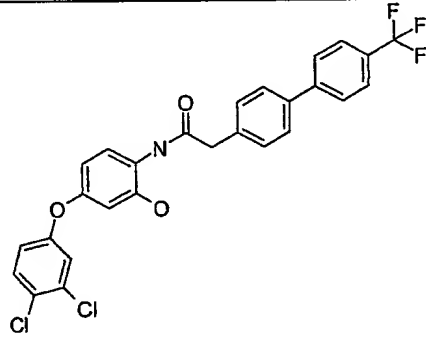
Example	Structure	Name
172		(2S)-[5-Bromo-2-dimethylcarbamoyloxy-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
173		(2S)-[5-Bromo-2-(3-morpholin-4-yl-propoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
174		(2S)-[5-Bromo-2-(4,4,4-trifluoro-butoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
175		(2S)-[5-Chloro-2-heptyloxy-benzoylamino]-3-(4'-cyclohexyl-biphenyl-4-yl)-propionic acid
176		(2S)-[5-Chloro-2-heptyloxy-benzoylamino]-3-(3',4'-dichloro-biphenyl-4-yl)-propionic acid

Example	Structure	Name
177		(2S)-(5-Bromo-2-butoxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
178		(2S)-[5-Bromo-2-(2-methyl-butoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
179		(2S)-(5-Bromo-2-cyclopropylmethoxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
180		(2S)-(5-Bromo-2-cyclopropylmethoxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
181		(2S)-[5-Bromo-2-(4-[1,2,4]triazol-1-yl-benzyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
182		(2S)-[5-Bromo-2-(isoquinolin-1-ylmethoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

Example	Structure	Name
183		(2S)-[2-(3-Benzoyloxy-benzoyloxy)-5-bromo-benzoylamino]-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
184		(2S)-[2-(3-Benzoyloxy-benzoyloxy)-5-bromo-benzoylamino]-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid
185		(2S)-[5-Bromo-2-(4-trifluoromethoxy-benzoyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
186		(2S)-[5-Bromo-2-(4-trifluoromethoxy-benzoyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
187		(2S)-[5-Bromo-2-(4-phenyl-butoxy)-benzoylamino]-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
188		(2S)-[5-Bromo-2-(6-phenyl-hexyloxy)-benzoylamino]-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester

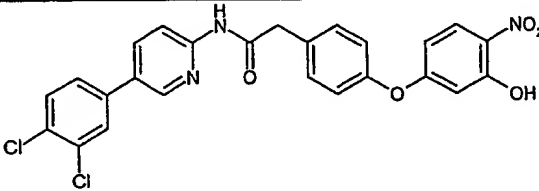
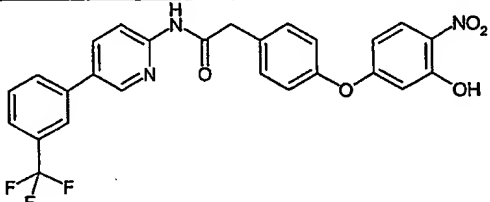
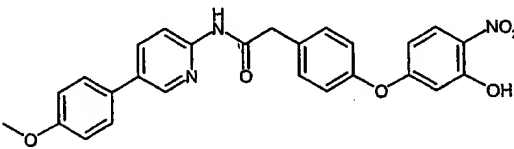
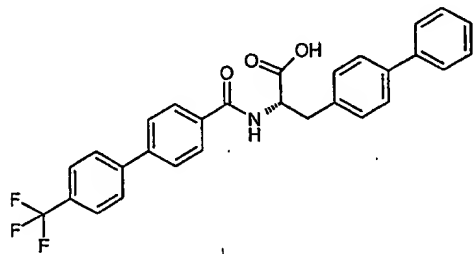
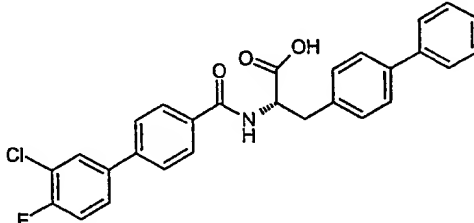


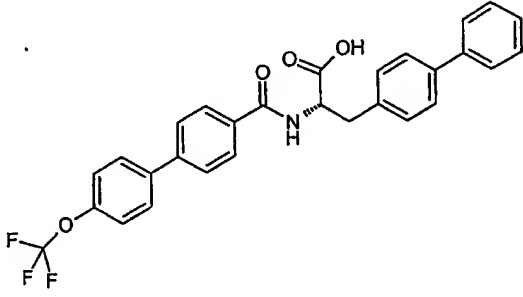
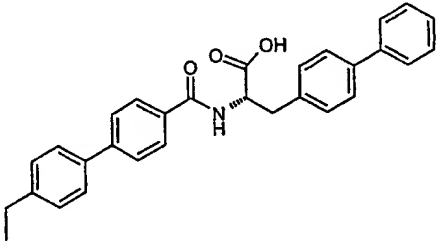
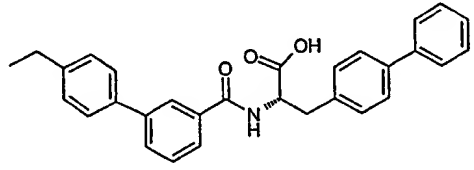
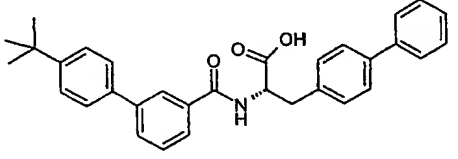
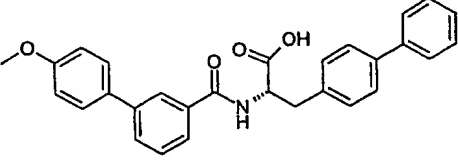
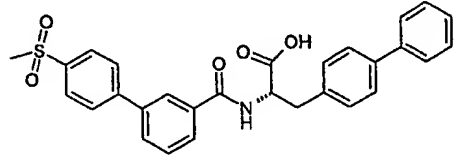
Example	Structure	Name
189		(2S)-(5-Chloro-2-heptyloxy-benzoylamino)-3-(4'-dimethylamino-biphenyl-4-yl)-propionic acid
190		(2S)-[5-Bromo-2-(4-phenyl-butoxy)-benzoylamino]-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid
191		(2S)-[5-Bromo-2-(6-phenyl-hexyloxy)-benzoylamino]-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid
192		(2S)-[5-Bromo-2-(2-cyclohexyl-ethoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
193		(2S)-[5-Bromo-2-(2-cyclohexyl-ethoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
194		(2S)-(5-Bromo-2-cyclohexylmethoxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

Example	Structure	Name
195		(2S)-(5-Bromo-2-cyclohexyloxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
196		(2S)-(5-Bromo-2-cyclohexyloxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
197		<i>N</i> -[2-Hydroxy-4-(4-trifluoromethyl-phenoxy)-phenyl]-2-(3'-methoxy-biphenyl-4-yl)-acetamide
198		<i>N</i> -[2-Hydroxy-4-(3,4-dichloro-phenoxy)-phenyl]-2-(4'-trifluoromethyl-biphenyl-4-yl)-acetamide

Example	Structure	Name
199		<i>N</i> -[2-Hydroxy-4-(2,4-dichloro-6-methyl-phenoxy)-phenyl]-2-(4'-trifluoromethyl-biphenyl-4-yl)-acetamide
200		<i>N</i> -[2-Hydroxy-4-(2,4-dichloro-6-methyl-phenoxy)-phenyl]-2-(3'-trifluoromethyl-biphenyl-4-yl)-acetamide
201		3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)- <i>N</i> -[4-(2,4-dichloro-6-methyl-phenoxy)-2-hydroxy-phenyl]-propionamide
202		<i>N</i> -[4-(2-Fluoro-6-methoxy-phenoxy)-2-hydroxy-phenyl]-3-(3'-methoxy-biphenyl-4-yl)-propionamide

Example	Structure	Name
203		N-[4-(2,4-Dichloro-6-methylphenoxy)-2-hydroxy-phenyl]-2-(4'-methoxy-biphenyl-4-yl)-acetamide
204		2-(3'-Chloro-4'-fluorobiphenyl-4-yl)-N-[4-(2,4-dichloro-6-methylphenoxy)-2-hydroxy-phenyl]-acetamide
205		2-Biphenyl-4-yl-N-[2-hydroxy-4-(4'-methoxy-biphenyl-4-yloxy)-phenyl]-acetamide
206		2-Biphenyl-4-yl-N-[2-hydroxy-4-(4'-trifluoromethylbiphenyl-4-yloxy)-phenyl]-acetamide
207		N-[4-(3,4-Dichlorophenoxy)-2-hydroxy-phenyl]-2-(3'-nitrobiphenyl-4-yl)-acetamide
208		N-[5-(3-Chlorophenyl)pyridin-2-yl]-2-[4-(3-hydroxy-4-nitrophenoxy)-phenyl]-acetamide

Example	Structure	Name
209		<i>N</i> -[5-(3,4-Dichloro-phenyl)-pyridin-2-yl]-2-[4-(3-hydroxy-4-nitro-phenoxy)-phenyl]-acetamide
210		<i>N</i> -[5-(3-Trifluoromethyl-phenyl)-pyridin-2-yl]-2-[4-(3-hydroxy-4-nitro-phenoxy)-phenyl]-acetamide
211		<i>N</i> -[5-(4-Methoxy-phenyl)-pyridin-2-yl]-2-[4-(3-hydroxy-4-nitro-phenoxy)-phenyl]-acetamide
212		3-Biphenyl-4-yl-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
213		3-Biphenyl-4-yl-(2S)-[(3'-chloro-4'-fluoro-biphenyl-4-carbonyl)-amino]-propionic acid

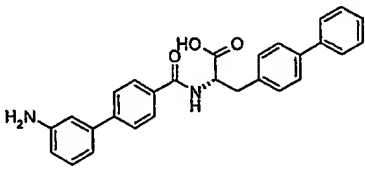
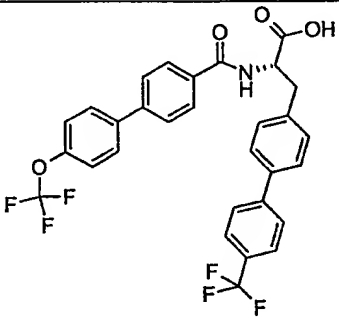
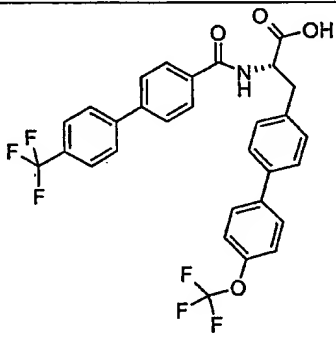
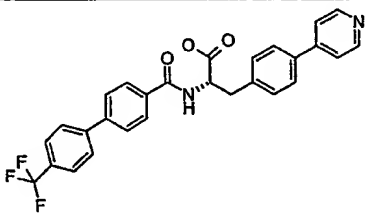
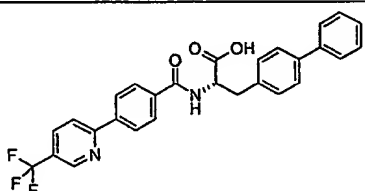
Example	Structure	Name
214		3-Biphenyl-4-yl-(2S)-[(4'-trifluoromethoxy-biphenyl-4-carbonyl)-amino]-propionic acid
215		3-Biphenyl-4-yl-(2S)-[(4'-ethyl-biphenyl-4-carbonyl)-amino]-propionic acid
216		3-Biphenyl-4-yl-(2S)-[(3'-ethyl-biphenyl-3-carbonyl)-amino]-propionic acid
217		3-Biphenyl-4-yl-(2S)-[(4'-tert-butylbiphenyl-3-carbonyl)-amino]-propionic acid
218		3-Biphenyl-4-yl-(2S)-[(4'-methoxy-biphenyl-3-carbonyl)-amino]-propionic acid
219		3-Biphenyl-4-yl-(2S)-[(4'-methane-sulfonyl-biphenyl-3-carbonyl)-amino]-propionic acid

Example	Structure	Name
220		3-Biphenyl-4-yl-(2S)-[(4'-tert-butyl-4-chloro-biphenyl-3-carbonyl)-amino]-propionic acid
221		(2S)-[(4-Chloro-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid
222		(2S)-[(4'-Methoxy-biphenyl-3-carbonyl)-amino]-3-(4'-methoxy-biphenyl-4-yl)-propionic acid
223		3-Biphenyl-4-yl-(2S)-[3-nitro-4-(3-trifluoromethylphenoxy)-benzoylamino]-propionic acid
224		3-(4'-Trifluoromethyl-biphenyl-4-yl)-(2S)-[4-(4-trifluoromethyl-phenoxy)-benzoylamino]-propionic acid
225		3-(4'-Trifluoromethyl-biphenyl-4-yl)-(2S)-[4-(5-trifluoromethyl-pyridin-2-yloxy)-benzoylamino]-propionic acid

Example	Structure	Name
226		3-[4-(4-Trifluoromethyl-phenoxy)-phenyl]-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
227		3-[4-(4-Cyano-phenoxy)-phenyl]-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
228		2S-(4-Benzoyloxy-benzoylamino)-3-biphenyl-4-yl-propionic acid
229		3-Biphenyl-4-yl-(2S)-[(4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid
230		3-Biphenyl-4-yl-(2S)-[(3-chloro-4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
231		3-Biphenyl-4-yl-(2S)-[4-(4-nitro-phenoxy)-benzoylamino]-propionic acid



Example	Structure	Name
232		3-Biphenyl-4-yl-(2S)-[4-(3,4-dimethyl-phenoxy)-3-nitro-benzoylamino]-propionic acid
233		3-Biphenyl-4-yl-(2S)-[(3'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
234		3-Biphenyl-4-yl-(2S)-[(3',5'-bis-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
235		3-Biphenyl-4-yl-(2S)-[(4'-tert-butyl-biphenyl-4-carbonyl)-amino]-propionic acid
236		3-Biphenyl-4-yl-(2S)-[(4'-dimethylamino-biphenyl-4-carbonyl)-amino]-propionic acid
237		3-Biphenyl-4-yl-(2S)-[(4'-methoxy-biphenyl-4-carbonyl)-amino]-propionic acid
238		3-Biphenyl-4-yl-2-[(3',4'-dichloro-biphenyl-4-carbonyl)-amino]-propionic acid
239		3-Biphenyl-4-yl-(2S)-[(5'-chloro-2'-methoxy-biphenyl-4-carbonyl)-amino]-propionic acid

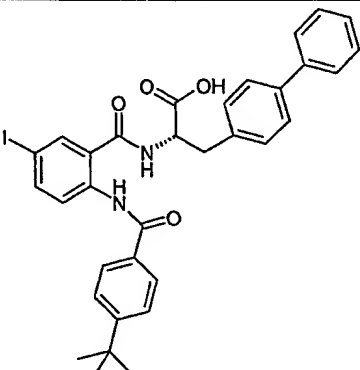
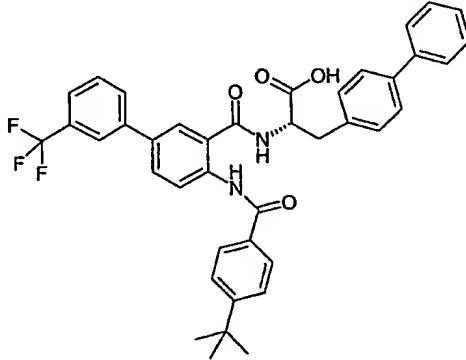
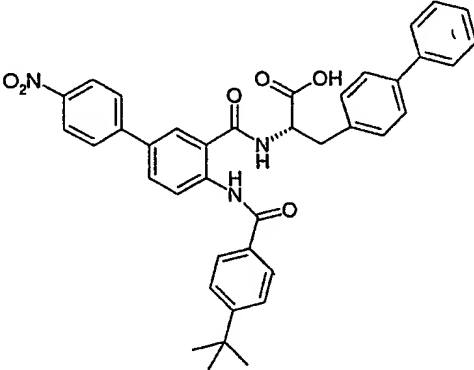
Example	Structure	Name
240		(2S)-[(3'-Amino-biphenyl-4-carbonyl)-amino]-3-biphenyl-4-yl-propionic acid
241		(2S)-[(4'-Trifluoromethoxy-biphenyl-4-carbonyl)-amino]-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid
242		3-(4'-Trifluoromethoxy-biphenyl-4-yl)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
243		3-(4-Pyridin-4-yl-phenyl)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
244		3-Biphenyl-4-yl-(2S)-[4-(5-trifluoromethyl-pyridin-2-yl)-benzoylamino]-propionic acid

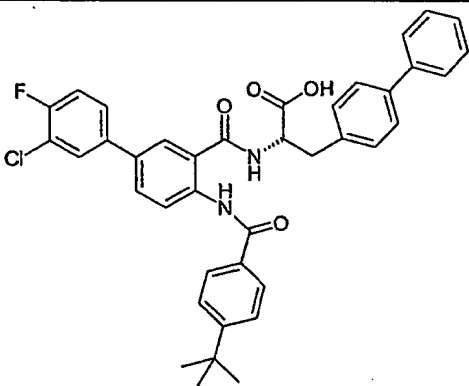
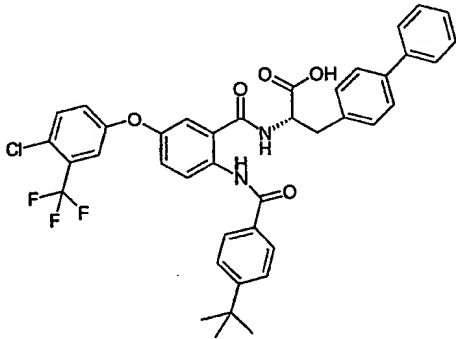
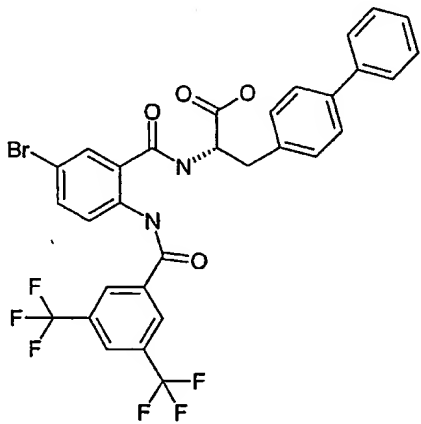
Example	Structure	Name
245		3-(4-Pyridin-4-yl-phenyl)-(2S)-[4-(5-trifluoromethyl-pyridin-2-yl)-benzoylamino]-propionic acid
246		3-(4'-Methanesulfonylamino-biphenyl-4-yl)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
247		3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
248		3-(4'-Cyano-biphenyl-4-yl)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
249		3-(5-Phenyl-pyridin-2-yl)-2-[(4'-trifluoromethoxy-biphenyl-4-carbonyl)-amino]-propionic acid
250		3-(4'-Amino-biphenyl-4-yl)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
251		3-(4'-Dimethylamino-biphenyl-4-yl)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid

Example	Structure	Name
252		3-(4'-Trifluoromethoxy-biphenyl-4-yl)-(2S)-[4-(5-trifluoromethyl-pyridin-2-yl)-benzoylamino]-propionic acid
253		3-(4'-Trifluoromethyl-biphenyl-4-yl)-(2S)-[4-(5-trifluoromethyl-pyridin-2-yl)-benzoylamino]-propionic acid
254		3-(4'-Trifluoromethoxy-biphenyl-4-yl)-(2S)-[4-(4-trifluoromethyl-phenoxy)-benzoylamino]-propionic acid
255		3-Biphenyl-4-yl-(2S)-[4-(4-trifluoromethyl-phenoxy)-benzoylamino]-propionic acid
256		3-Biphenyl-4-yl-(2S)-[4-(4-formyl-phenoxy)-benzoylamino]-propionic acid
257		3-(5'-Chloro-2'-methoxy-biphenyl-4-yl)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
258		3-(4'-Chloro-biphenyl-4-yl)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid

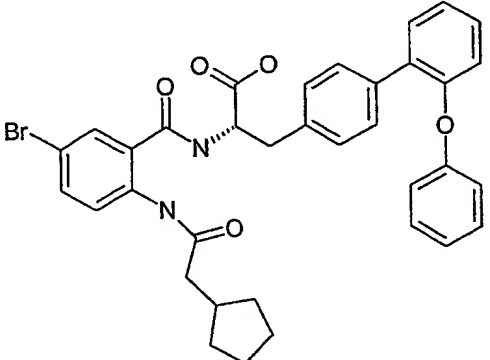
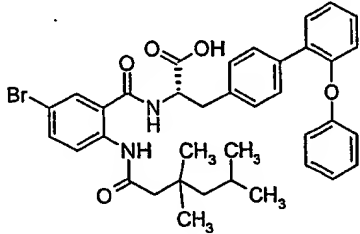
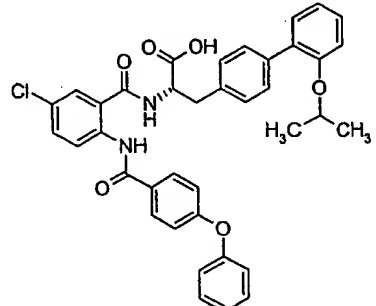
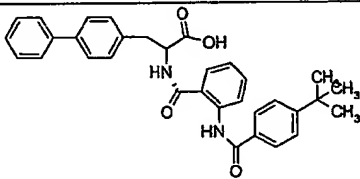
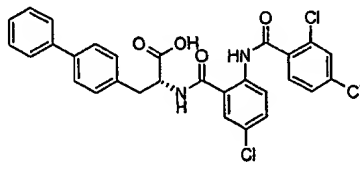
Example	Structure	Name
259		3-Biphenyl-4-yl-(2R)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
260		3-(5-Phenyl-pyridin-2-yl)-2-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
261		3-(3'-Acetylamino-biphenyl-4-yl)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
262		3-(3',4'-Dichloro-biphenyl-4-yl)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
263		3-(5'-Fluoro-2'-methoxy-biphenyl-4-yl)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
264		3-[4'-(Acetylamino-methyl)-biphenyl-4-yl)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
265		3-(4'-Trifluoromethoxy-biphenyl-4-yl)-(2S)-[4-(5-trifluoromethyl-pyridin-2-yloxy)-benzoylamino]-propionic acid

Example	Structure	Name
266		3-Biphenyl-4-yl-(2S)-[4-(5-trifluoromethyl-pyridin-2-yloxy)-benzoylamino]-propionic acid
267		3-[4-(4-Nitro-phenoxy)-phenyl]-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
268		3-[4-(4-Formyl-phenoxy)-phenyl]-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
269		3-(4-Thiophen-3-yl-phenyl)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
270		3-(4-Thiophen-3-yl-phenyl)-(2S)-[(4'-trifluoromethoxy-biphenyl-4-carbonyl)-amino]-propionic acid
271		(2S)-(4-Benzoyloxy-benzoylamino)-3-(4'-trifluoromethoxy-biphenyl-4-yl)-propionic acid
272		3-(2'-Phenoxy-biphenyl-4-yl)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
273		3-(4'-Phenoxy-biphenyl-4-yl)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid

Example	Structure	Name
274		3-Biphenyl-4-yl-(2S)-[2-(4- <i>tert</i> -butyl-benzoylamino)-5-iodo-benzoyl-amino]-propionic acid
275		3-Biphenyl-4-yl-(2S)-[[4-(4- <i>tert</i> -butyl-benzoylamino)-3'-trifluoromethyl-biphenyl-3-carbonyl]-amino]-propionic acid
276		3-Biphenyl-4-yl-(2S)-[[4-(4- <i>tert</i> -butyl-benzoylamino)-4'-nitro-phenyl-3-carbonyl]-amino]-propionic acid

Example	Structure	Name
277		3-Biphenyl-4-yl-(2S)-{[4-(4- <i>tert</i> -butyl-benzoylamino)-3'-chloro-4'-fluoro-biphenyl-3-carbonyl]-amino}-propionic acid
278		3-Biphenyl-4-yl-(2S)-[4-(4- <i>tert</i> -butyl-benzoylamino)-5-(4-chloro-3-trifluoromethyl-phenoxy)-benzoylamino]-propionic acid
279		3-Biphenyl-4-yl-(2S)-[2-(3,5-bis-trifluoromethyl-benzoylamino)-5-bromo-benzoylamino]-propionic acid

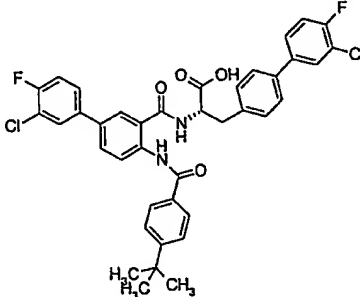
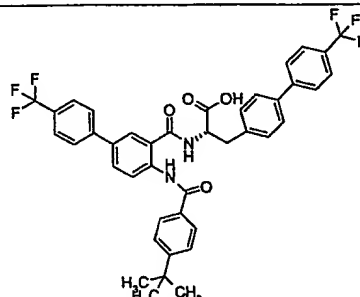
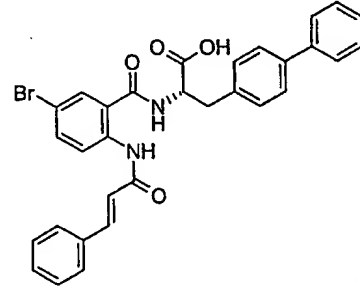
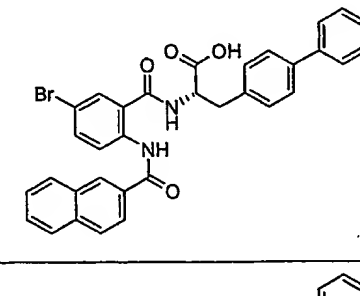
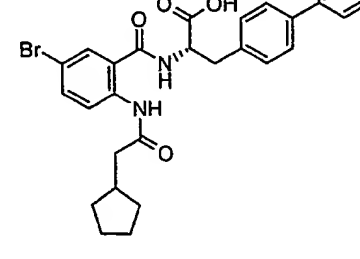


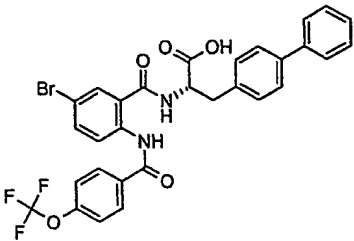
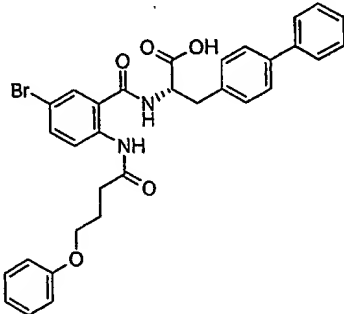
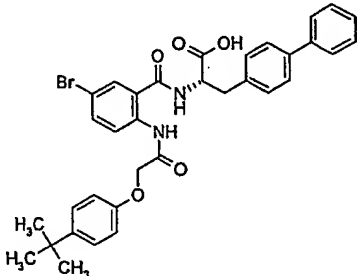
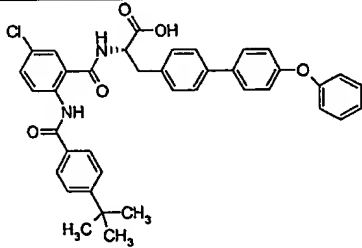
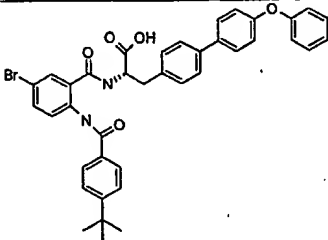
Example	Structure	Name
280		(2S)-[5-bromo-2-(2-cyclopentyl-acetylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
281		(2S)-[5-Bromo-2-(3,3,5-trimethyl-hexanoylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
282		(2S)-[5-Chloro-2-(4-phenoxy-benzoylamino)-benzoylamino]-3-(2'-isopropoxy-biphenyl-4-yl)-propionic acid
283		3-Biphenyl-4-yl-(2S)-[2-(4-tert-butyl-benzoylamino)-benzoylamino]-propionic acid
284		3-Biphenyl-4-yl-(2S)-[5-chloro-2-(2,4-dichloro-benzoylamino)-benzoylamino]-propionic acid

Example	Structure	Name
285		(2S)-({4-[(Biphenyl-4-carbonyl)-amino]-3'-chloro-4'-fluoro-biphenyl-3-carbonyl)-amino}-3-biphenyl-4-yl-propionic acid
286		(2S)-{2-[(Biphenyl-4-carbonyl)-amino]-benzoylamino}-3-(3'-chloro-4'-fluoro-biphenyl-4-yl)-propionic acid
287		(2S)-[2-(4-tert-Butyl-benzoylamino)-benzoylamino]-3-(3'-chloro-4'-fluoro-biphenyl-4-yl)-propionic acid
288		3-Biphenyl-4-yl-(2S)-[5-bromo-2-(4-tert-butyl-benzoylamino)-benzoylamino]-propionic acid

Example	Structure	Name
289		3-Biphenyl-4-yl-(2S)-{[4-(4-tert-butyl-benzoylamino)-4'-cyano-biphenyl-3-carbonyl]-amino}-propionic acid
290		(2S)-{[4'-Amino-4-(4-tert-butyl-benzoylamino)-biphenyl-3-carbonyl]-amino}-3-biphenyl-4-yl-propionic acid
291		3-Biphenyl-4-yl-(2S)-{[4-(4-tert-butyl-benzoylamino)-3'-cyano-biphenyl-3-carbonyl]-amino}-propionic acid
292		(2S)-{[3-[(Biphenyl-4-carbonyl)-amino]-naphthalene-2-carbonyl]-amino}-3-(3'-chloro-4'-fluoro-biphenyl-4-yl)-propionic acid
293		(2S)-{[3-(4-tert-Butyl-benzoylamino)-naphthalene-2-carbonyl]-amino}-3-(3'-chloro-4'-fluoro-biphenyl-4-yl)-propionic acid

Example	Structure	Name
294		(2S)-{[3'-Aminomethyl-4-(4-tert-butyl-benzoylamino)-biphenyl-3-carbonyl]-amino}-3-biphenyl-4-yl-propionic acid
295		3-Biphenyl-4-yl-(2S)-{[4-(4-tert-butyl-benzoylamino)-4'-carbamimidoyl-biphenyl-3-carbonyl]-amino}-propionic acid
296		3-Biphenyl-4-yl-(2S)-[2-(4-tert-butyl-benzoylamino)-5-(4-nitro-phenoxy)-benzoylamino]-propionic acid
297		(2S)-{[4-(4-tert-Butyl-benzoylamino)-3'-trifluoromethyl-biphenyl-3-carbonyl]-amino}-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionic acid

Example	Structure	Name
298		(2S)-[4-(4-tert-Butyl-benzoylamino)-3'-chloro-4'-fluoro-biphenyl-3-carbonyl]-amino-3-(3'-chloro-4'-fluoro-biphenyl-4-yl)-propionic acid
299		(2S)-[4-(4-tert-Butyl-benzoylamino)-4'-trifluoromethyl-biphenyl-3-carbonyl]-amino-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid
300		3-Biphenyl-4-yl-(2S)-[5-bromo-2-(3-phenyl-acryloylamino)-benzoylamino]-propionic acid
301		3-Biphenyl-4-yl-(2S)-[5-bromo-2-[(naphthalene-2-carbonyl)-amino]-benzoylamino]-propionic acid
302		3-Biphenyl-4-yl-(2S)-[5-bromo-2-(2-cyclopentyl-acetylamino)-benzoylamino]-propionic acid

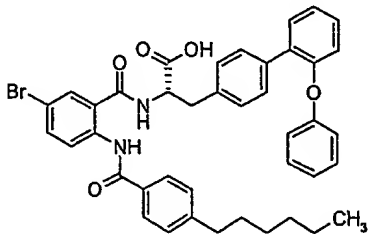
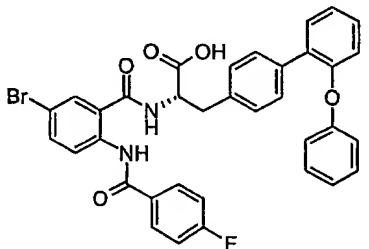
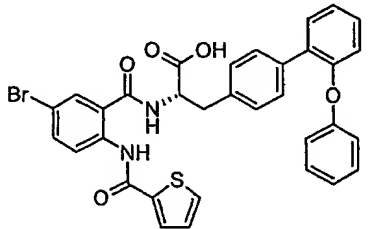
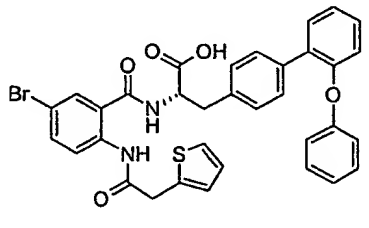
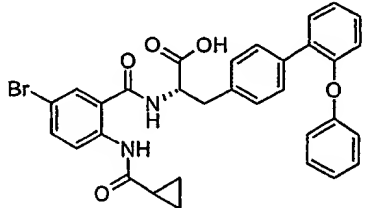
Example	Structure	Name
303		3-Biphenyl-4-yl-(2S)-[5-bromo-2-(4-trifluoromethoxy-benzoylamino)-benzoylamino]-propionic acid
304		3-Biphenyl-4-yl-(2S)-[5-bromo-2-(4-phenoxy-butylamino)-benzoylamino]-propionic acid
305		3-Biphenyl-4-yl-(2S)-[5-bromo-2-[2-(4-tert-butyl-phenoxy)-acetylamino]-benzoylamino]-propionic acid
306		(2S)-[2-(4-tert-Butyl-benzoylamino)-5-chloro-benzoylamino]-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid
307		2-[5-Bromo-(2S)-(4-tert-butyl-benzoylamino)-benzoylamino]-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid

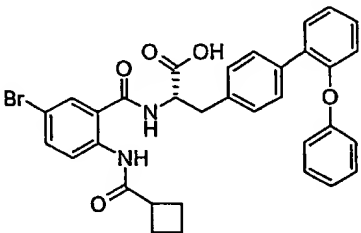
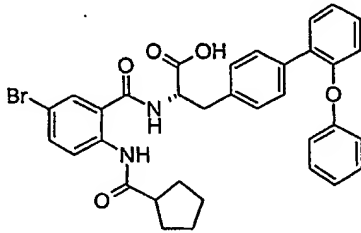
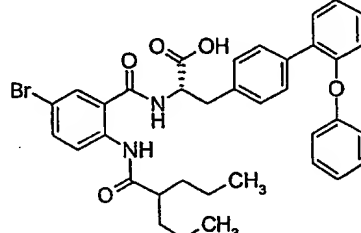
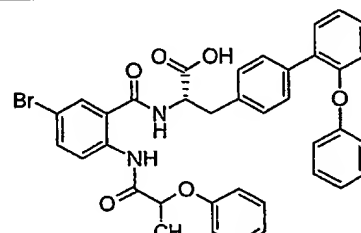
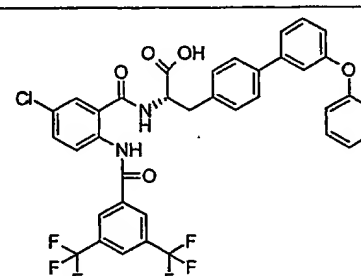
Example	Structure	Name
308		3-Biphenyl-4-yl-(2S)-[4-chloro-2-(4-trifluoromethyl-benzoylamino)-benzoylamino]-propionic acid
309		3-Biphenyl-4-yl-(2S)-[2-(4-tert-butyl-benzoylamino)-5-(4-trifluoromethyl-phenoxy)-benzoylamino]-propionic acid
310		3-Biphenyl-4-yl-(2S)-[2-(4-trifluoromethyl-benzoylamino)-5-(4-trifluoromethyl-phenoxy)-benzoylamino]-propionic acid
311		3-Biphenyl-4-yl-(2S)-[2-(4-tert-butyl-benzoylamino)-4-(4-trifluoromethyl-phenoxy)-benzoylamino]-propionic acid
312		(2S)-[2-(4-tert-Butyl-benzoylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

Example	Structure	Name
313		(2S)-[5-Chloro-2-(4-phenoxy-benzoylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
314		(2S)-[2-(4-Benzyloxy-benzoylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
315		(2S)-[5-Bromo-2-phenylacetyl-amino-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
316		(2S)-[5-Bromo-2-(4-bromo-benzoylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
317		(2S)-[5-Bromo-2-[2-(4-fluoro-phenyl)-acetyl-amino]-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid



Example	Structure	Name
318		2-{5-Bromo-(2S)-[(naphthalene-2-carbonyl)-amino]-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
319		(2S)-{5-Bromo-2-[(naphthalene-1-carbonyl)-amino]-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
320		(2S)-{5-Chloro-2-(3-phenoxy-benzoylamino)-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
321		-S-[2-(3-Benzoyloxy-benzoylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
322		(2S)-{5-Bromo-2-(4-phenoxy-benzoylamino)-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

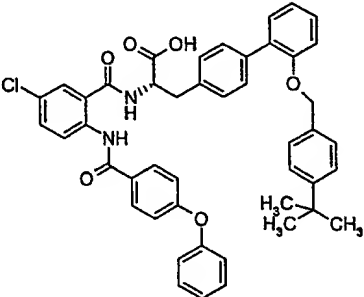
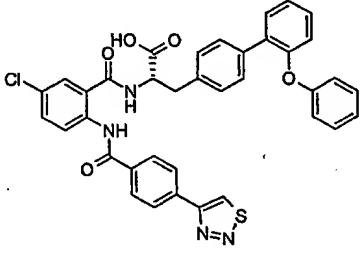
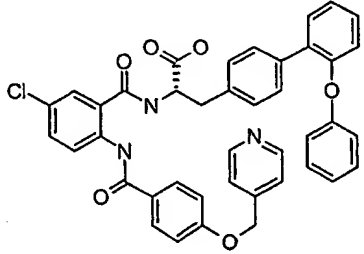
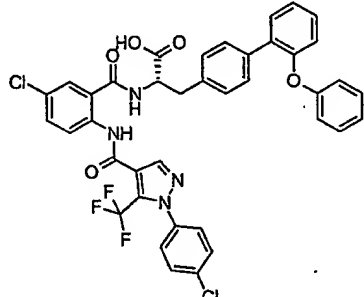
Example	Structure	Name
323		(2S)-[5-Bromo-2-(4-hexyl-benzoylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
324		(2S)-[5-Bromo-2-(4-fluoro-benzoylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
325		(2S)-[5-Bromo-2-[(thiophene-2-carbonyl)-amino]-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
326		(2S)-[5-Bromo-2-(2-thiophen-2-yl-acetylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
327		(2S)-[5-Bromo-2-(cyclopropanecarbonyl-amino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

Example	Structure	Name
328		(2S)-[5-Bromo-2-(cyclobutanecarbonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
329		(2S)-[5-Bromo-2-(cyclopentanecarbonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
330		(2S)-[5-Bromo-2-(2-propylpentanoylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
331		(2S)-[5-Bromo-2-(2-phenoxypropionylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
332		(2S)-[2-(3,5-Bis-trifluoromethyl-5-chloro-benzoylamino)-5-chloro-benzoylamino]-3-(3'-phenoxy-biphenyl-4-yl)-propionic acid

Example	Structure	Name
333		(2S)-[5-Bromo-2-(3,4,5-trimethoxy-benzoylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
334		(2S)-{2-[(Adamantane-1-carbonyl)-amino]-5-bromo-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
335		(2S)-(5-Bromo-2-[[1-(4-chloro-phenyl)-cyclopropanecarbonyl]-amino]-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
336		(2S)-(5-Bromo-2-[[1-(2,4-dichloro-phenyl)-cyclopropanecarbonyl]-amino]-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
337		(2S)-{5-Bromo-2-[(2,2-dichloro-1-methyl-cyclopropanecarbonyl)-amino]-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

Example	Structure	Name
338		(2S)-{5-Chloro-2-[(6-chloro-pyridine-3-carbonyl)-amino]-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
339		(2S)-{5-Chloro-2-[[1-(4-trifluoromethyl-pyrimidin-2-yl)-piperidine-4-carbonyl]-amino]-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
340		(2S)-{5-Bromo-2-[(1-phenyl-cyclopropanecarbonyl)-amino]-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
341		(2S)-{5-Bromo-2-[(2-phenyl-cyclopropanecarbonyl)-amino]-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
342		(2S)-{5-Chloro-2-(2-phenoxy-benzoylamino)-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

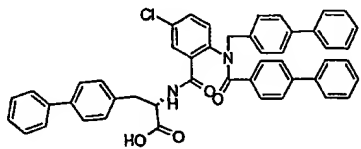
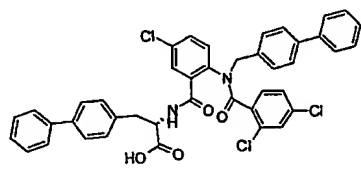
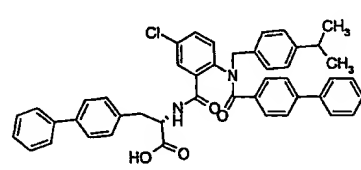
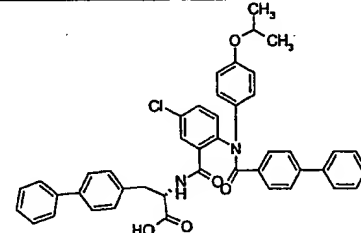
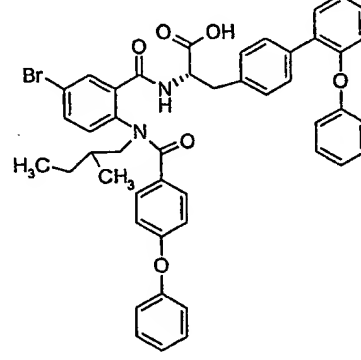
Example	Structure	Name
343		3-(2'-Benzyloxy-biphenyl-4-yl)-(2S)-[2-(3,5-bis-trifluoromethyl-benzoylamino)-5-chloro-benzoylamino]-propionic acid
344		(2S)-[5-Chloro-2-[(6-phenoxy-pyridine-3-carbonyl)-amino]-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
345		(2S)-[5-Chloro-2-(4-phenoxy-benzoylamino)-benzoylamino]-3-(2'-cyclopentyloxy-biphenyl-4-yl)-propionic acid
346		(2S)-[5-Chloro-2-(4-phenoxy-benzoylamino)-benzoylamino]-3-[2'-(4-trifluoromethyl-benzyloxy)-biphenyl-4-yl]-propionic acid

Example	Structure	Name
347		3-[2'-(4-tert-Butyl-benzyloxy)-biphenyl-4-yl]-(2S)-[5-chloro-2-(4-phenoxy-benzoylamino)-benzoylamino]-propionic acid
348		(2S)-[5-Chloro-2-(4-[1,2,3]thiadiazol-4-yl-benzoylamino)benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
349		(2S)-[5-Chloro-2-[4-(pyridin-4-ylmethoxy)-benzoylamino]-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
350		(2S)-[5-Chloro-2-[[1-(4-chloro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino]-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

Example	Structure	Name
351		(2S)-(5-Chloro-2-([1-(4-chloro-phenyl)-5-propyl-1H-pyrazole-4-carbonyl]-amino)-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
352		(2S)-[5-Bromo-2-(3-phenyl-propionylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
353		(2S)-[2-(3,5-Bis-trifluoromethyl-benzoylamino)-5-chloro-benzoylamino]-3-[2'-(4-pentyl-phenoxy)-biphenyl-4-yl]-propionic acid
354		(2S)-{2-[(Benzofuran-2-carbonyl)-amino]-5-bromo-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
355		(2S)-{2-[(Benzo[b]thiophene-2-carbonyl)-amino]-5-bromo-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

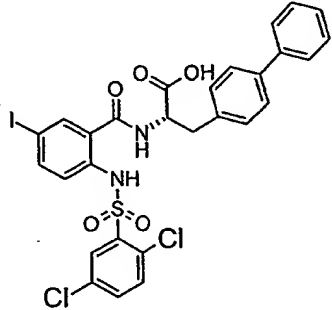
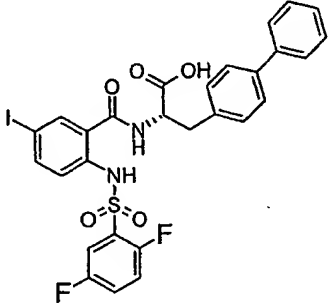
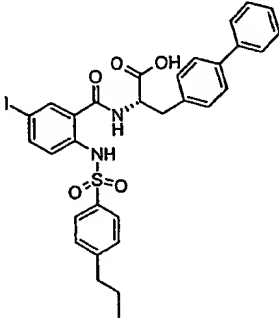
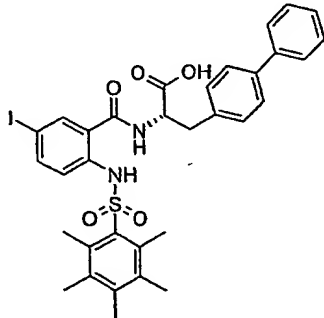


Example	Structure	Name
356		(2S)-{5-Bromo-2-[(3-chloro-benzo[b]thiophene-2-carbonyl)-amino]-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
357		(2S)-{2-[(3,5-Bis-trifluoromethyl-benzoyl)-pentyl-amino]-5-chloro-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
358		(2S)-{2-[(Biphenyl-4-carbonyl)-(4-methyl-benzyl)-amino]-5-chloro-benzoylamino}-3-biphenyl-4-yl-propionic acid
359		3-Biphenyl-4-yl-(2S){5-chloro-2-[(3,5-dichloro-benzoyl)-(4-methyl-benzyl)-amino]-benzoylamino}-propionic acid
360		(2S)-{2-[(Biphenyl-4-carbonyl)-(3-phenyl-propyl)-amino]-5-chloro-benzoylamino}-3-biphenyl-4-yl-propionic acid
361		3-Biphenyl-4-yl-(2S)-{5-chloro-2-[(2,4-dichloro-benzoyl)-(3-phenyl-propyl)-amino]-benzoylamino}-propionic acid

Example	Structure	Name
362		(2S)-2-[(Biphenyl-4-carbonyl)-biphenyl-4-ylmethyl-amino]-5-chloro-benzoylamino-3-biphenyl-4-yl-propionic acid
363		3-Biphenyl-4-yl-(2S)-2-[biphenyl-4-ylmethyl-(2,4-dichloro-benzoyl)-amino]-5-chloro-benzoylamino}-propionic acid
364		(2S)-2-[(Biphenyl-4-carbonyl)-(4-isopropyl-benzyl)-amino]-5-chloro-benzoylamino-3-biphenyl-4-yl-propionic acid
365		(2S)-2-[(Biphenyl-4-carbonyl)-(4-isopropoxy-benzyl)-amino]-5-chloro-benzoylamino-3-biphenyl-4-yl-propionic acid
366		(2S)-{5-Bromo-2-[(2-methyl-butyl)-(4-phenoxy-benzoyl)-amino]-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

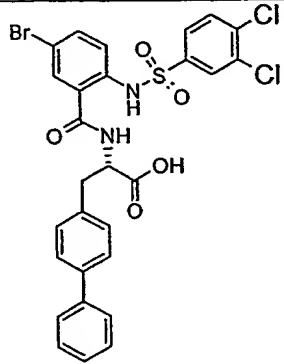
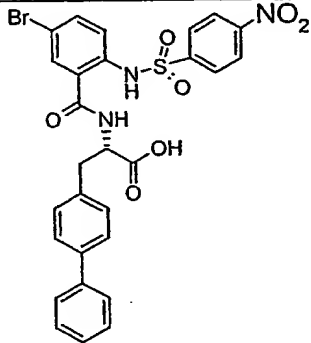
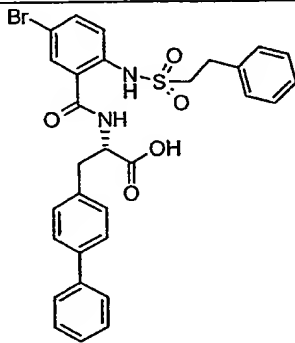
Example	Structure	Name
367		(2S)-[5-Chloro-2-(5-dibutylamino-naphthalene-1-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
368		(2S)-[5-Bromo-2-(4-tert-butyl-benzenesulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
369		(2S)-[5-Bromo-2-(4-tert-butyl-benzenesulfonylamino)-benzoylamino]-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid
370		3-Biphenyl-4-yl-(2S)-[2-(3,4-dichloro-benzenesulfonylamino)-5-iodo-benzoylamino]-propionic acid

Example	Structure	Name
371		(2S)-{2-[(Biphenyl-4-sulfonyl)-(4-methyl-benzyl)-amino]-5-chloro-benzoylamino}-3-biphenyl-4-yl-propionic acid
372		(2S)-[2-(Biphenyl-4-sulfonylamino)-5-chloro-benzoylamino]-3-biphenyl-4-yl-propionic acid
373		3-Biphenyl-4-yl-(2S)[2-(4-tert-butyl-benzenesulfonylamino)-5-iodo-benzoylamino]-propionic acid
374		3-Biphenyl-4-yl-(2S)[[4-(4-tert-butyl-benzenesulfonylamino)-3'-chloro-4'-fluoro-biphenyl-3-carbonyl]-amino]-propionic acid
375		3-Biphenyl-4-yl-(2S)[5-iodo-2-(2,4,5-trichloro-benzenesulfonylamino)-benzoylamino]-propionic acid

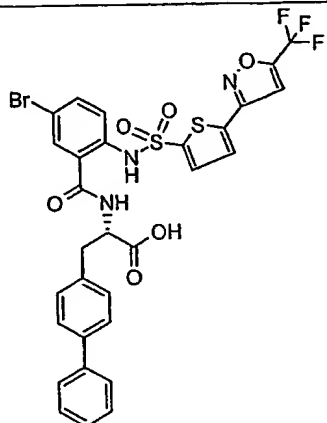
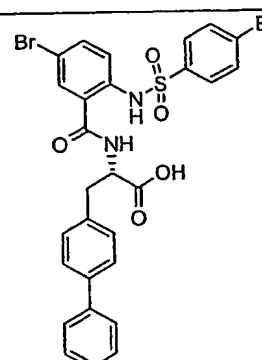
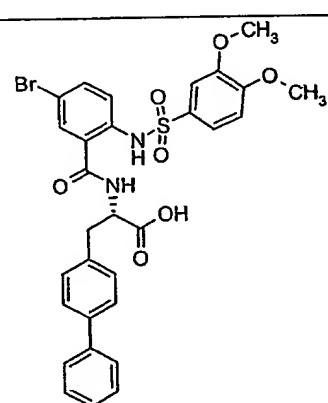
Example	Structure	Name
376		3-Biphenyl-4-yl-(2S)-[2-(2,5-dichloro-benzenesulfonylamino)-5-iodo-benzoylamino]-propionic acid
377		3-Biphenyl-4-yl-(2S)-[2-(2,4-difluoro-benzenesulfonylamino)-5-iodo-benzoylamino]-propionic acid
378		3-Biphenyl-4-yl-(2S)-[5-iodo-2-(4-propyl-benzenesulfonylamino)-benzoylamino]-propionic acid
379		3-Biphenyl-4-yl-(2S)-[5-iodo-2-pentamethylbenzenesulfonylamino-benzoylamino]-propionic acid

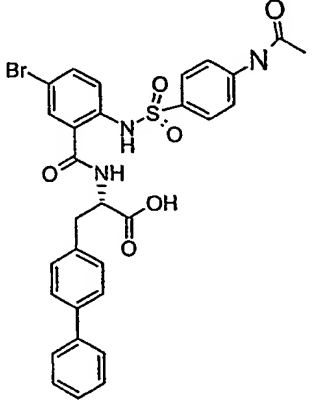
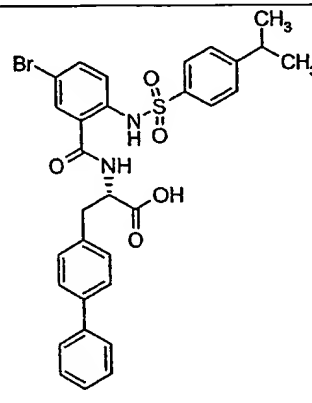
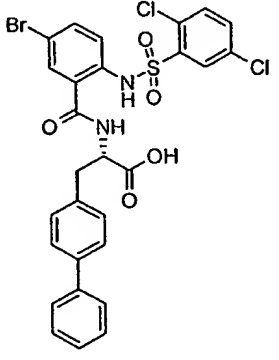
Example	Structure	Name
380		3-Biphenyl-4-yl-(2S)-[5-iodo-2-(toluene-4-sulfonylamino)-benzoylamino]-propionic acid
381		3-Biphenyl-4-yl-(2S)-[2-(4-bromo-benzenesulfonylamino)-5-iodo-benzoylamino]-propionic acid
382		3-Biphenyl-4-yl-(2S)-[5-iodo-2-(naphthalene-2-sulfonylamino)-benzoylamino]-propionic acid
383		3-Biphenyl-4-yl-(2S)-[5-bromo-2-(4-tert-butyl-benzenesulfonylamino)-benzoylamino]-propionic acid

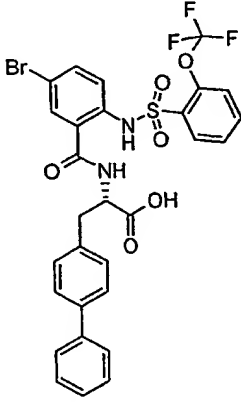
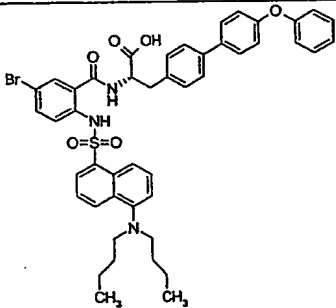
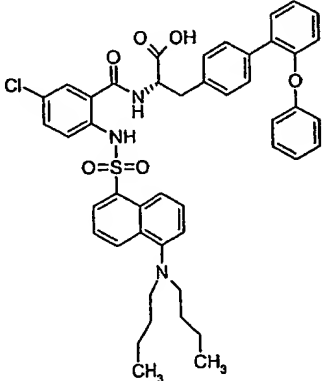
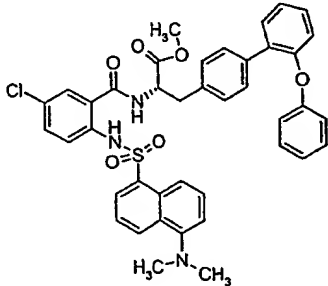
Example	Structure	Name
384		2-[5-Acetylamino-(2S)-(4-tert-butyl-benzenesulfonylamino)-benzoylamino]-3-biphenyl-4-yl-propionic acid
385		3-Biphenyl-4-yl-(2R)-[5-bromo-2-(4-tert-butyl-benzenesulfonylamino)-benzoylamino]-propionic acid methyl ester
386		3-Biphenyl-4-yl-(2S)-[5-bromo-2-(6-morpholin-4-yl-pyridine-3-sulfonylamino)-benzoylamino]-propionic acid
387		3-Biphenyl-4-yl-(2S)-[5-bromo-2-(4-vinyl-benzenesulfonylamino)-benzoylamino]-propionic acid

Example	Structure	Name
388		3-Biphenyl-4-yl-(2S)-[5-bromo-2-(3,4-dichlorobenzenesulfonylamino)-benzoylamino]-propionic acid
389		3-Biphenyl-4-yl-(2S)-[5-bromo-2-(4-nitrobenzenesulfonylamino)-benzoylamino]-propionic acid
390		3-Biphenyl-4-yl-(2S)-[5-bromo-2-(2-phenylethenesulfonylamino)-benzoylamino]-propionic acid



Example	Structure	Name
391		3-Biphenyl-4-yl-(2S)-[5-bromo-2-[5-(5-trifluoromethyl-isoxazol-3-yl)-thiophene-2-sulfonylamino]-benzoylamino]-propionic acid
392		3-Biphenyl-4-yl-(2S)-[5-bromo-2-(4-bromobenzenesulfonylamino)-benzoylamino]-propionic acid
393		3-Biphenyl-4-yl-(2S)-[5-bromo-2-(3,4-dimethoxybenzenesulfonylamino)-benzoylamino]-propionic acid

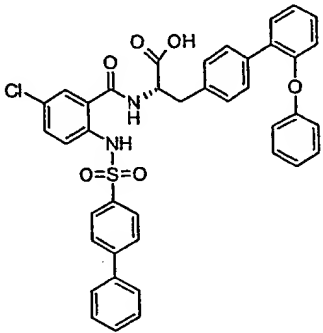
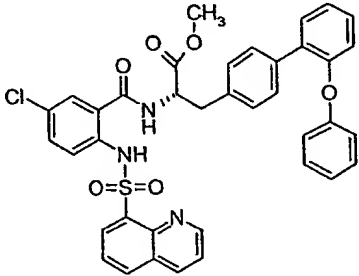
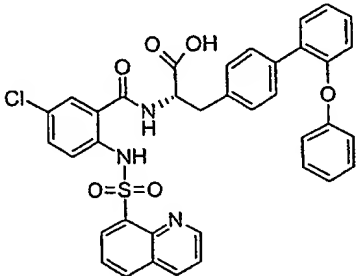
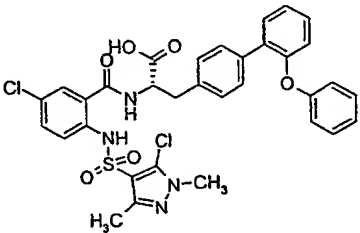
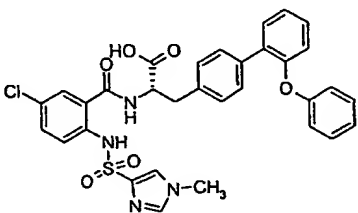
Example	Structure	Name
394		(2S)-[2-(4-Acetylamino-benzenesulfonylamino)-5-bromo-benzoylamino]-3-biphenyl-4-yl-propionic acid
395		3-Biphenyl-4-yl-(2S)-[5-bromo-2-(4-isopropyl-benzenesulfonylamino)-benzoylamino]-propionic acid
396		3-Biphenyl-4-yl-(2S)-[5-bromo-2-(2,5-dichloro-benzenesulfonylamino)-benzoylamino]-propionic acid

Example	Structure	Name
397		3-Biphenyl-4-yl-(2S)-[5-bromo-2-(2-trifluoromethoxy-benzenesulfonylamino)-benzoylamino]-propionic acid
398		(2S)-[5-Bromo-2-(5-dibutylamino-naphthalene-1-sulfonylamino)-benzoylamino]-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid
399		(2S)-[5-Chloro-2-(5-dibutylamino-naphthalene-1-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
400		(2S)-[5-Chloro-2-(5-dimethylamino-naphthalene-1-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester

Example	Structure	Name
401		(2S)-[5-Bromo-2-(5-dimethylamino-naphthalene-1-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
402		(2S)-[5-Chloro-2-(5-dimethylamino-naphthalene-1-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
403		(2S)-[5-Bromo-2-(5-dimethylamino-naphthalene-1-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
404		(2S)-[5-Bromo-2-(5-dibutylamino-naphthalene-1-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

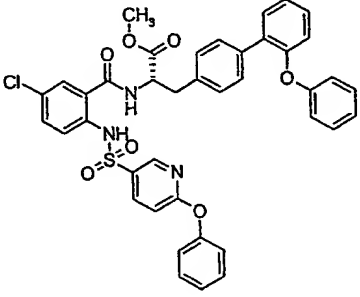
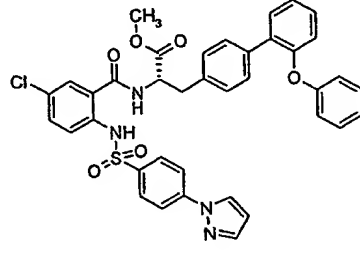
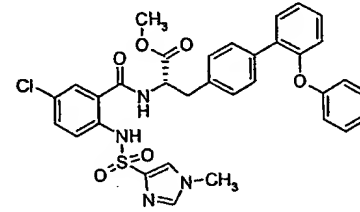
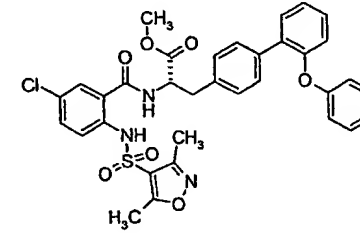
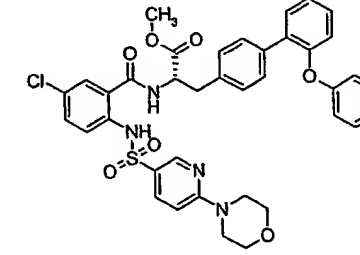
Example	Structure	Name
405		(2S)-(2-benzenesulfonylamino-5-chloro-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
406		(2S)-(2-benzenesulfonylamino-5-chloro-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
407		(2S)-[5-chloro-2-(naphthalene-1-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
408		(2S)-[5-chloro-2-(naphthalene-1-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
409		(2S)-[5-chloro-2-(naphthalene-2-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester

Example	Structure	Name
410		(2S)-[5-Chloro-2-(naphthalene-2-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
411		(2S)-[2-(4-tert-Butyl-benzenesulfonylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
412		(2S)-[2-(4-tert-Butyl-benzenesulfonylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
413		(2S)-[2-(Biphenyl-4-sulfonylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester

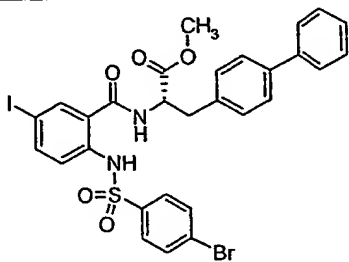
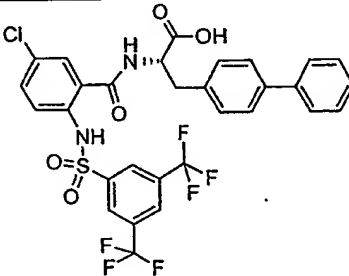
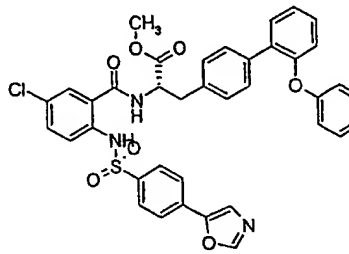
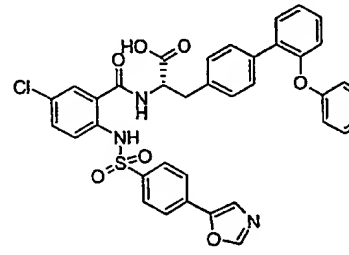
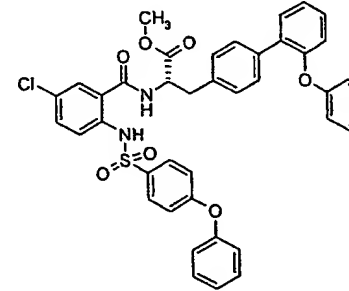
Example	Structure	Name
414		(2S)-[2-(Biphenyl-4-sulfonylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
415		(2S)-[5-Chloro-2-(quinoline-8-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
416		(2S)-[5-Chloro-2-(quinoline-8-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
417		(2S)-[5-Chloro-2-(5-chloro-1,3-dimethyl-1H-pyrazole-4-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
418		(2S)-[5-Chloro-2-(1-methyl-1H-imidazole-4-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

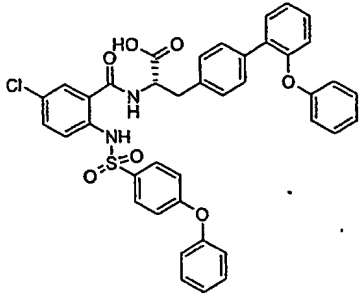
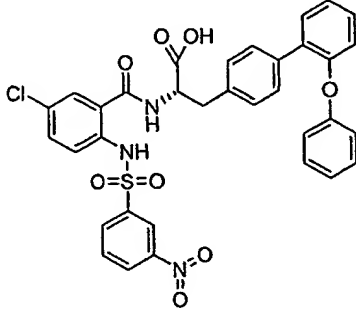
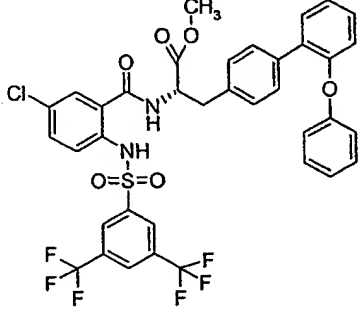
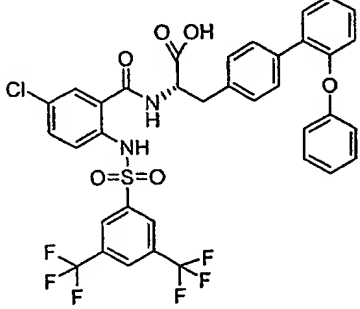
Example	Structure	Name
419		(2S)-[5-Chloro-2-(6-phenoxy-pyridine-3-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
420		(2S)-[5-Chloro-2-(4-pyrazol-1-yl-benzenesulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
421		(2S)-[5-Chloro-2-(5-chloro-1,3-dimethyl-1H-pyrazole-4-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
422		(2S)-[5-Chloro-2-[3-(5-methyl-[1,3,4]oxadiazol-2-yl)-benzenesulfonylamino]-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester

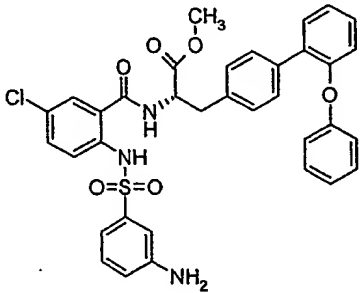
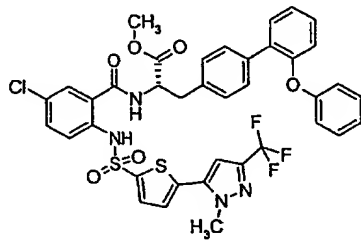
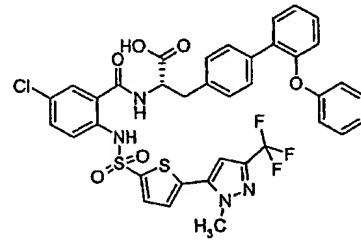
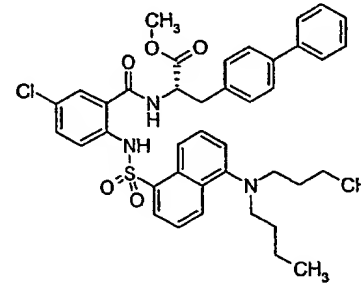


Example	Structure	Name
423		(2S)-[5-Chloro-2-(6-phenoxy-pyridine-3-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
424		(2S)-[5-Chloro-2-(4-pyrazol-1-yl-benzenesulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
425		(2S)-[5-Chloro-2-(1-methyl-1H-imidazole-4-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
426		(2S)-[5-Chloro-2-(3,5-dimethyl-isoxazole-4-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
427		(2S)-[5-Chloro-2-(6-morpholin-4-yl-pyridine-3-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester

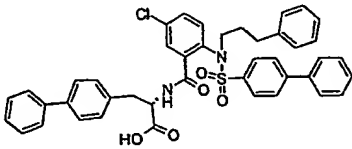
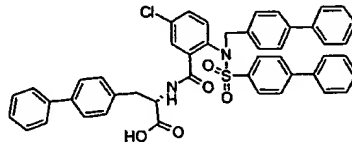
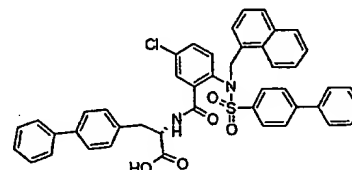
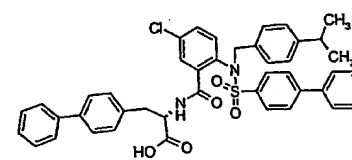
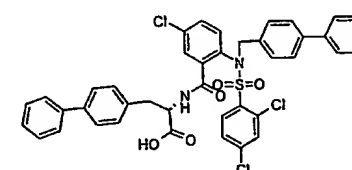
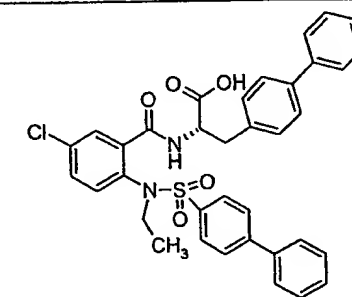
Example	Structure	Name
428		(2S)-[5-Chloro-2-(6-morpholin-4-yl-pyridine-3-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
429		(2S)-[5-Chloro-2-[5-(2-methylsulfanyl-pyrimidin-4-yl)-thiophene-2-sulfonylamino]-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
430		(2S)-[5-Chloro-2-[5-(2-methylsulfanyl-pyrimidin-4-yl)-thiophene-2-sulfonylamino]-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
431		(2S)-[5-Chloro-2-[4-(5-methyl-[1,3,4]oxadiazol-2-yl)-benzenesulfonylamino]-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
432		3-Biphenyl-4-yl-(2S)-[2-(2,5-dichloro-benzenesulfonylamino)-5-iodo-benzoylamino]-propionic acid methyl ester

Example	Structure	Name
433		3-Biphenyl-4-yl-(2S)-[2-(4-bromo-benzenesulfonylamino)-5-iodo-benzoylamino]-propionic acid methyl ester
434		3-Biphenyl-4-yl-(2S)-[2-(3,5-bis-trifluoromethyl-benzenesulfonylamino)-5-chloro-benzoylamino]-propionic acid
435		(2S)-[5-Chloro-2-(4-oxazol-5-yl-benzenesulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
436		(2S)-[5-Chloro-2-(4-oxazol-5-yl-benzenesulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
437		(2S)-[5-Chloro-2-(4-phenoxy-benzenesulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester

Example	Structure	Name
438		(2S)-[5-Chloro-2-(4-phenoxy-benzenesulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
439		(2S)-[5-Chloro-2-(3-nitro-benzenesulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
440		(2S)-[2-(3,5-Bis-trifluoromethyl-benzenesulfonylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
441		(2S)-[2-(3,5-Bis-trifluoromethyl-benzenesulfonylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

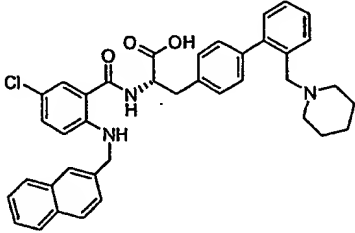
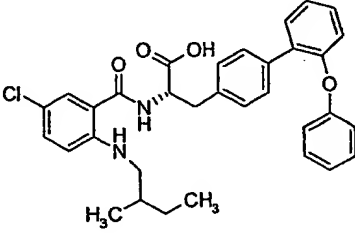
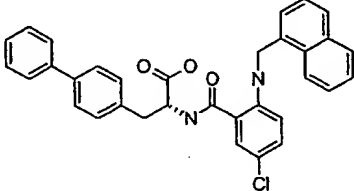
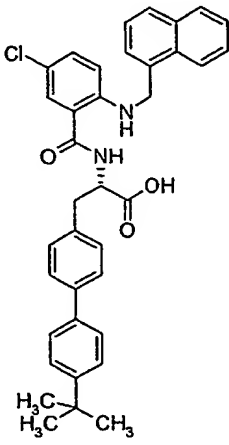
Example	Structure	Name
442		(2S)-[2-(3-Amino-benzenesulfonylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
443		(2S)-{5-Chloro-2-[5-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yl)-thiophene-2-sulfonylamino]-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
444		(2S)-{5-Chloro-2-[5-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yl)-thiophene-2-sulfonylamino]-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
445		3-Biphenyl-4-yl-(2S)-[5-chloro-2-(5-dibutylamino-naphthalene-1-sulfonylamino)-benzoylamino]-propionic acid methyl ester

Example	Structure	Name
446		3-Biphenyl-4-yl-(2S)-[5-chloro-2-(5-dibutylamino-naphthalene-1-sulfonylamino)-benzoylamino]-propionic acid
447		(2S)-[5-Bromo-2-(4-tert-butyl-benzenesulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
448		(2S)-[5-Bromo-2-(4-tert-butyl-benzenesulfonylamino)-benzoylamino]-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester
449		3-Biphenyl-4-yl-(2S)-[5-chloro-2-[naphthalen-1-ylmethyl-(4-nitro-benzenesulfonyl)-amino]-benzoylamino]-propionic acid
450		(2S)-2-[(Biphenyl-4-sulfonyl)-(3-methyl-thiophen-2-ylmethyl)-amino]-5-chloro-benzoylamino-3-biphenyl-4-yl-propionic acid

Example	Structure	Name
451		(2S)-2-[(Biphenyl-4-sulfonyl)-(3-phenyl-propyl)-amino]-5-chloro-benzoylamino-3-biphenyl-4-yl-propionic acid
452		(2S)-2-[(Biphenyl-4-sulfonyl)-biphenyl-4-ylmethyl-amino]-5-chloro-benzoylamino-3-biphenyl-4-yl-propionic acid
453		(2S)-2-[(Biphenyl-4-sulfonyl)-naphthalen-1-ylmethyl-amino]-5-chloro-benzoylamino-3-biphenyl-4-yl-propionic acid
454		(2S)-2-[(Biphenyl-4-sulfonyl)-(4-isopropyl-benzyl)-amino]-5-chloro-benzoylamino-3-biphenyl-4-yl-propionic acid
455		3-Biphenyl-4-yl-(2S)-2-[biphenyl-4-ylmethyl-(2,4-dichloro-benzenesulfonyl)-amino]-5-chloro-benzoylamino-propionic acid
456		(2S)-2-[(Biphenyl-4-sulfonyl)-ethyl-amino]-5-chloro-benzoylamino-3-biphenyl-4-yl-propionic acid

Example	Structure	Name
457		(2S)-2-[(Biphenyl-4-sulfonyl)-ethyl-amino]-5-iodo-benzoylamino-3-biphenyl-4-yl-propionic acid
458		2-[5-Chloro-2-[(naphthalen-1-ylmethyl)-amino]-benzoylamino]-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid
459		(S)-2-[2-[3-(4-tert-Butylphenoxy)-benzylamino]-5-chloro-benzoylamino]-3-(4'-cyclohexyl-biphenyl-4-yl)-propionic acid
460		(2S)-[5-Chloro-2-[(naphthalen-1-ylmethyl)-amino]-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

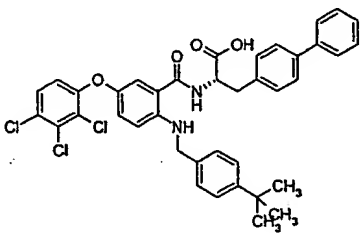
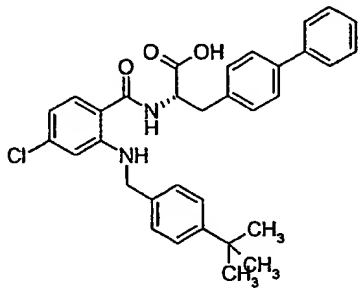
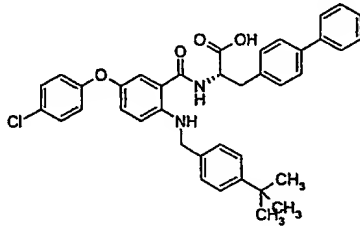
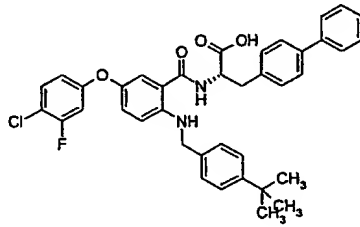
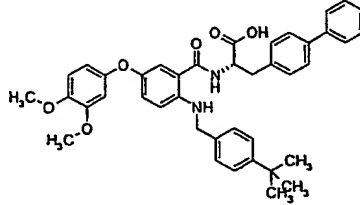


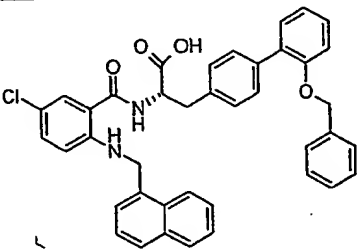
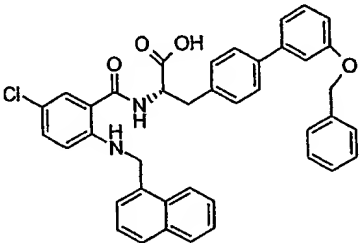
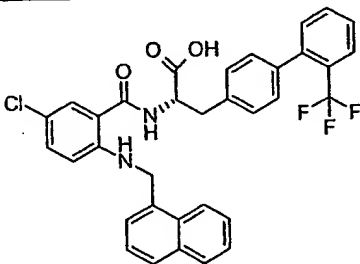
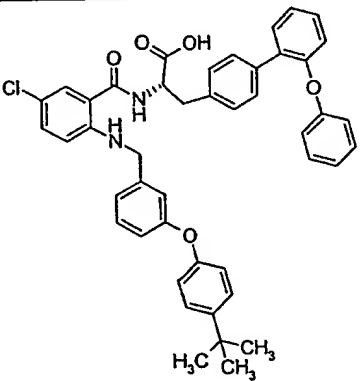
Example	Structure	Name
461		(2S)-{5-Chloro-2-[(naphthalen-2-ylmethyl)-amino]-benzoylamino}-3-(2'-piperidin-1-ylmethyl-biphenyl-4-yl)-propionic acid
462		2S-[5-Chloro-2-(2-methyl-butylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
463		3-Biphenyl-4-yl-2S-{5-chloro-2-[(naphthalen-1-ylmethyl)-amino]-benzoylamino}-propionic acid
464		3-(4'-tert-Butyl-biphenyl-4-yl)-(2S)-{5-chloro-2-[(naphthalen-1-ylmethyl)-amino]-benzoylamino}-propionic acid

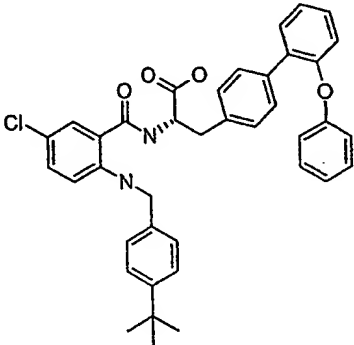
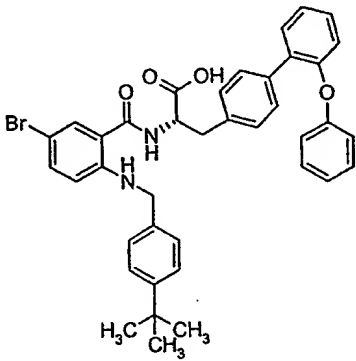
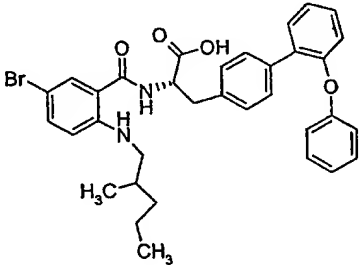
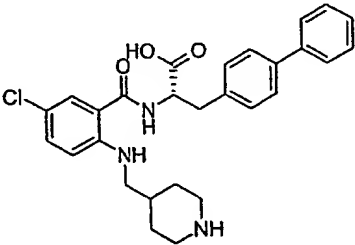
Example	Structure	Name
465		(2S)-{5-Chloro-2-[(naphthalen-1-ylmethyl)-amino]-benzoylamino}-3-(4'-methanesulfonyl-biphenyl-4-yl)-propionic acid
466		(2S)-(5-Chloro-2-hexylamino-benzoylamino)-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid
467		(2S)-(5-Chloro-2-hexylamino-benzoylamino)-3-(4'-dimethylamino-biphenyl-4-yl)-propionic acid
468		(2S)-[2-(4-tert-Butyl-benzylamino)-5-chloro-benzoylamino]-3-(4'-dimethylamino-biphenyl-4-yl)-propionic acid

Example	Structure	Name
469		(2S)-{2-[3-(4-tert-Butylphenoxy)-benzylamino]-5-chloro-benzoylamino}-3-(4'-dimethylamino-biphenyl-4-yl)-propionic acid
470		(2S)-{5-Chloro-2-[(naphthalen-1-ylmethyl)-amino]-benzoylamino}-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid
471		(2S)-[2-(4-tert-Butylbenzylamino)-5-chloro-benzoylamino]-3-(4'-cyclohexyl-biphenyl-4-yl)-propionic acid
472		(2S)-{5-Chloro-2-heptylamino-benzoylamino}-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid
473		(2S)-{5-Chloro-2-heptylamino-benzoylamino}-3-(4'-cyclohexyl-biphenyl-4-yl)-propionic acid
474		(2S)-{5-Chloro-2-[(naphthalen-1-ylmethyl)-amino]-benzoylamino}-3-(4'-cyclohexyl-biphenyl-4-yl)-propionic acid

Example	Structure	Name
475		(2S)-{5-Chloro-2-[(naphthalen-1-ylmethyl)-amino]-benzoylamino}-3-(4'-pentyl-biphenyl-4-yl)-propionic acid
476		(2S)-[2-(4-tert-Butyl-benzylamino)-5-iodo-benzoylamino]-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid
477		3-(4'-Amino-biphenyl-4-yl)-2S-{5-chloro-2-[(naphthalen-1-ylmethyl)-amino]-benzoylamino}-propionic acid
478		3-Biphenyl-4-yl-2S-[2-(4-tert-butyl-benzylamino)-5-(3,4-dichloro-phenoxy)-benzoylamino]-propionic acid
479		3-Biphenyl-4-yl-2S-[2-(4-tert-butyl-benzylamino)-5-(3-chloro-4-fluoro-phenoxy)-benzoylamino]-propionic acid
480		3-Biphenyl-4-yl-(2S)-[2-(4-tert-butyl-benzylamino)-5-(3-trifluoromethyl-phenoxy)-benzoylamino]-propionic acid

Example	Structure	Name
481		3-Biphenyl-4-yl-(2S)-[2-(4-tert-butyl-benzylamino)-5-(2,3,4-trichloro-phenoxy)-benzoylamino]-propionic acid
482		3-Biphenyl-4-yl-(2S)-[2-(4-tert-butyl-benzylamino)-4-chloro-benzoylamino]-propionic acid
483		3-Biphenyl-4-yl-(2S)-[2-(4-tert-butyl-benzylamino)-5-(4-chloro-phenoxy)-benzoylamino]-propionic acid
484		3-Biphenyl-4-yl-2S-[2-(4-tert-butyl-benzylamino)-5-(4-chloro-3-fluoro-phenoxy)-benzoylamino]-propionic acid
485		3-Biphenyl-4-yl-(2S)-[2-(4-tert-butyl-benzylamino)-5-(3,4-dimethoxy-phenoxy)-benzoylamino]-propionic acid

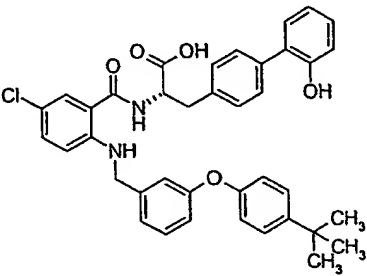
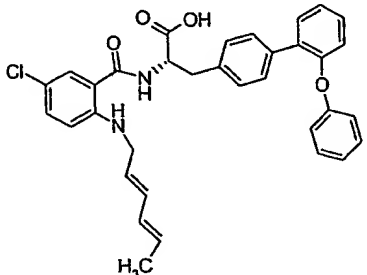
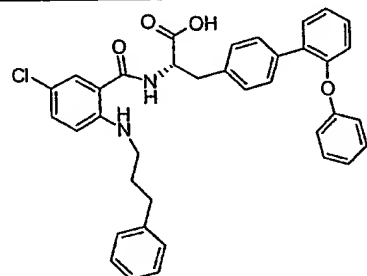
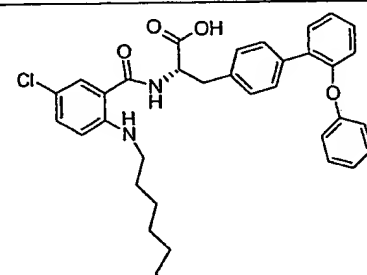
Example	Structure	Name
486		3-(2'-Benzyloxy-biphenyl-4-yl)-(2S)-{5-chloro-2-[(naphthalen-1-ylmethyl)-amino]-benzoylamino}-propionic acid
487		3-(3'-Benzyloxy-biphenyl-4-yl)-(2S)-{5-chloro-2-[(naphthalen-1-ylmethyl)-amino]-benzoylamino}-propionic acid
488		(2S)-{5-Chloro-2-[(naphthalen-1-ylmethyl)-amino]-benzoylamino}-3-(2'-trifluoromethyl-biphenyl-4-yl)-propionic acid
489		(2S)-{2-[3-(4-tert-Butylphenoxy)-benzylamino]-5-chloro-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

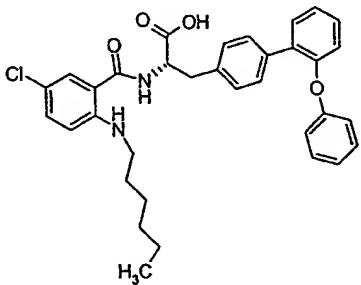
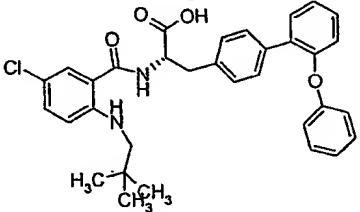
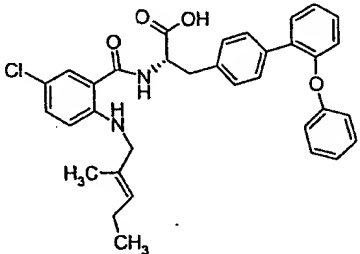
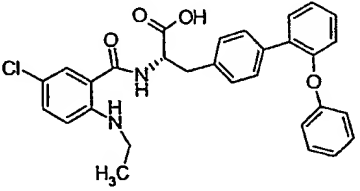
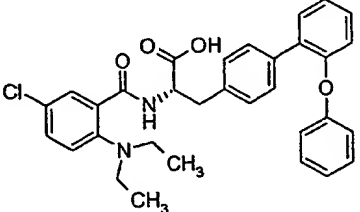
Example	Structure	Name
490		(2S)-[2-(4-tert-Butyl-benzylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
491		(2S)-[5-Bromo-2-(4-tert-butyl-benzylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
492		(2S)-[5-Bromo-2-(2-methyl-pentylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
493		3-Biphenyl-4-yl-(2S)-{5-chloro-2-[(piperidin-4-ylmethyl)-amino]-benzoylamino}-propionic acid

Example	Structure	Name
494		3-(2'-Benzyloxy-biphenyl-4-yl)-(2S)-[2-[3-(4-tert-butylphenoxy)-benzylamino]-5-chloro-benzoylamino]-propionic acid
495		3-(2'-Benzyloxy-biphenyl-4-yl)-(2S)-[2-(4-tert-butylbenzylamino)-5-chloro-benzoylamino]-propionic acid
496		(2S)-[5-Chloro-2-(3-phenoxybenzylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
497		(2S)-[2-(3,5-Bis-trifluoromethyl-benzylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
498		(2S)-[5-Chloro-2-(4-phenoxybenzylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

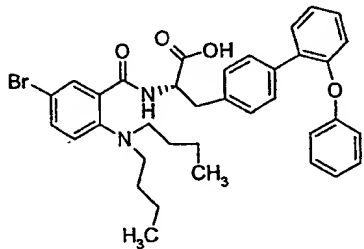
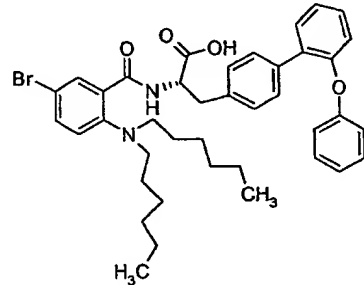
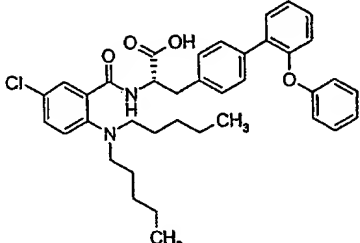
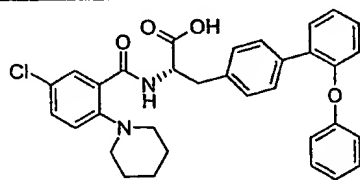
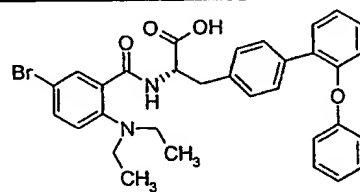
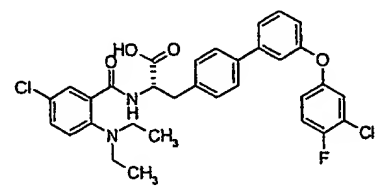


Example	Structure	Name
499		(2S)-[2-(4-Benzoyloxy-benzylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
500		3-Biphenyl-4-yl-(2S)-[5-(2-chloro-4-trifluoromethyl-phenoxy)-2-(2-methyl-butylamino)-benzoylamino]-propionic acid
501		(2S)-[3,5-Dichloro-2-(2-methyl-butylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
502		(2S)-[5-Bromo-2-(cyclohexylmethyl-amino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
503		(2S)-[5-Chloro-2-pentylamino-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

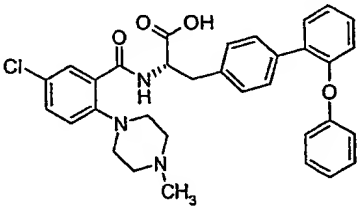
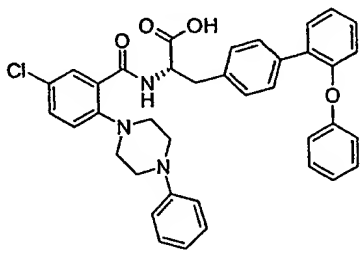
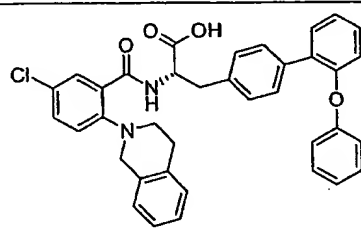
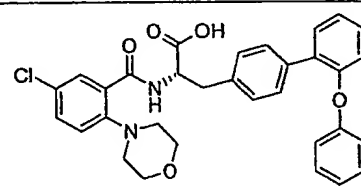
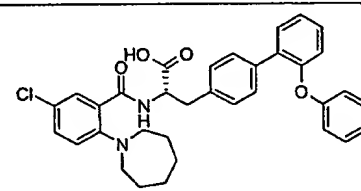
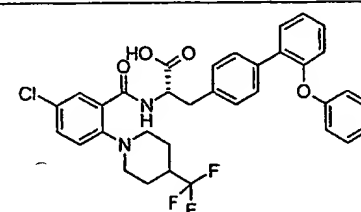
Example	Structure	Name
504		(2S)-{2-[3-(4-tert-Butylphenoxy)-benzylamino]-5-chloro-benzoylamino}-3-(2'-hydroxy-biphenyl-4-yl)-propionic acid
505		(2S)-{5-Chloro-2-hexa-2,4-dienylamino-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
506		(2S)-[5-Chloro-2-(3-phenylpropylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
507		(2S)-{5-Chloro-2-octylamino-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

Example	Structure	Name
508		(2S)-(5-Chloro-2-hexylamino-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
509		(2S)-[5-Chloro-2-(2,2-dimethyl-propylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
510		(2S)-[5-Chloro-2-(2-methyl-pent-2-enylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
511		(2S)-(5-Chloro-2-ethylamino-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
512		: (2S)-(5-Chloro-2-diethylamino-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

Example	Structure	Name
513		2-(5-Chloro-2-diethylamino-benzoylamino)-3-[3'-(4-trifluoromethyl-phenoxy)-biphenyl-4-yl]-propionic acid
514		(2S)-[5-Chloro-2-(3,5-dimethyl-piperidin-1-yl)-benzoylamino]-3-[2'-phenoxy-biphenyl-4-yl]-propionic acid
515		3-Biphenyl-4-yl-(2S)-[2-[bis-(4-benzyloxy-benzyl)-amino]-5-chloro-benzoylamino]-propionic acid
516		3-Biphenyl-4-yl-(2S)-[2-(bis-naphthalen-1-ylmethyl-amino)-5-chloro-benzoylamino]-propionic acid
517		3-Biphenyl-4-yl-(2S)-[2-(bis-biphenyl-4-ylmethyl-amino)-5-chloro-benzoylamino]-propionic acid

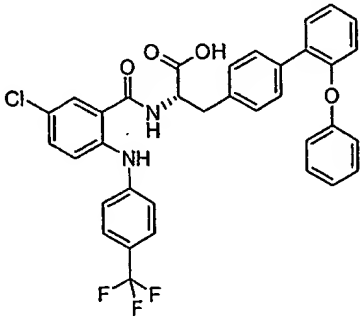
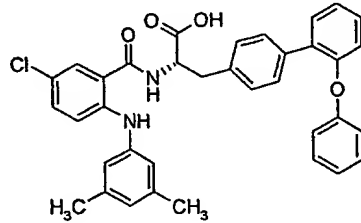
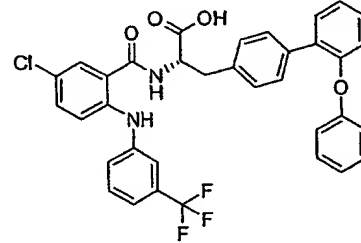
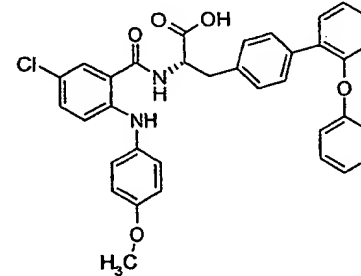
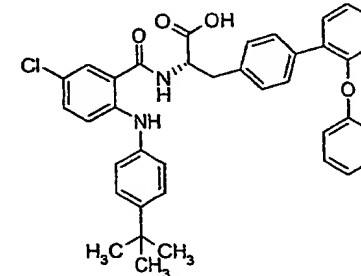
Example	Structure	Name
518		(2S)-(5-Bromo-2-dibutylamino-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
519		(2S)-(5-Bromo-2-dihexylamino-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
520		(2S)-(5-Chloro-2-dipentylamino-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
521		(2S)-(5-Chloro-2-piperidin-1-yl-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
522		(2S)-(5-Bromo-2-diethylamino-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
523		(2S)-(5-Chloro-2-diethylamino-benzoylamino)-3-[3'-(3-chloro-4-fluorophenoxy)-biphenyl-4-yl]-propionic acid

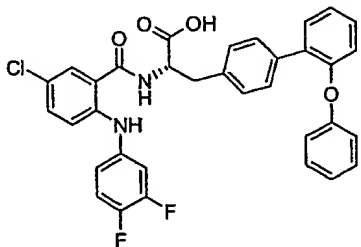
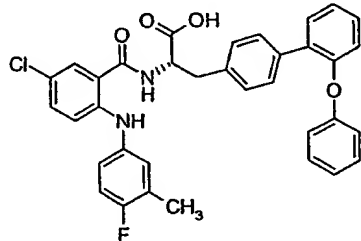
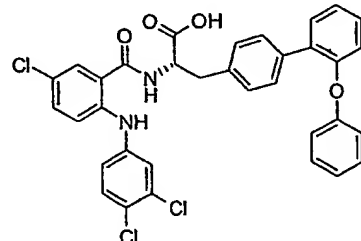
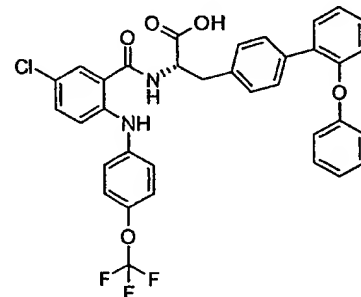
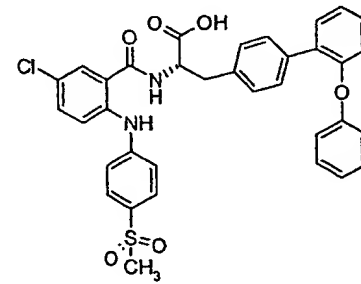
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524		(2S)-(5-Bromo-2-piperidin-1-yl-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
525		(2S)-(5-Chloro-2-diethylamino-benzoylamino)-3-[3'-(4-methoxy-phenoxy)-biphenyl-4-yl]-propionic acid
526		(2S)-(5-Chloro-2-diethylamino-benzoylamino)-3-[3'-(4-trifluoromethoxy-phenoxy)-biphenyl-4-yl]-propionic acid
527		3-[3'-(4-tert-Butyl-phenoxy)-biphenyl-4-yl]-(2S)-(5-chloro-2-diethylamino-benzoylamino)-propionic acid
528		(2S)-(5-Bromo-2-diethylamino-benzoylamino)-3-[3'-(4-trifluoromethyl-phenoxy)-biphenyl-4-yl]-propionic acid
529		(2S)-(5-Bromo-2-diethylamino-benzoylamino)-3-[3'-(3-fluoro-phenoxy)-biphenyl-4-yl]-propionic acid
530		(2S)-(5-Bromo-2-pyrrolidin-1-yl-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

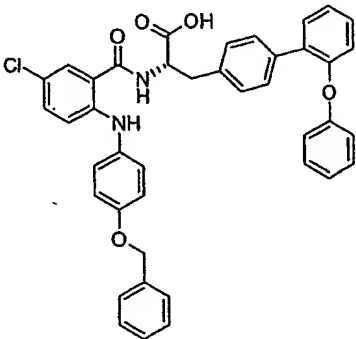
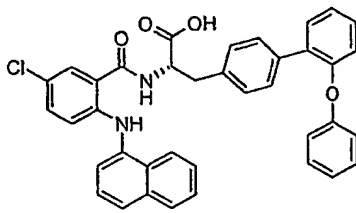
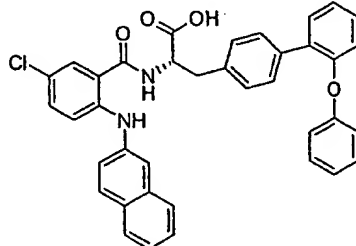
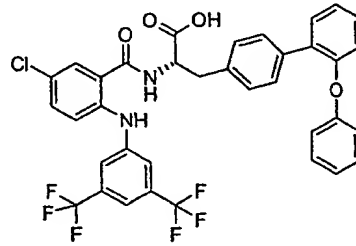
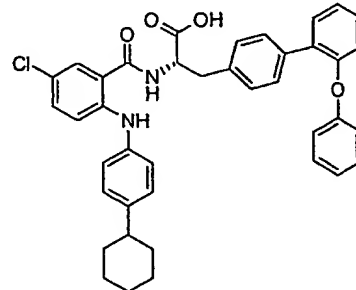
Example	Structure	Name
531		(2S)-[5-Chloro-2-(4-methyl-piperazin-1-yl)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
532		(2S)-[5-Chloro-2-(4-phenyl-piperazin-1-yl)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
533		(2S)-[5-Chloro-2-(3,4-dihydro-1H-isoquinolin-2-yl)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
534		(2S)-[5-Chloro-2-morpholin-4-yl-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
535		(2S)-[2-Azepin-1-yl-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
536		(2S)-[5-Chloro-2-(4-trifluoromethyl-piperidin-1-yl)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

Example	Structure	Name
537		(2S)-[5-Chloro-2-(4-methylsulfanyl-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
538		(2S)-[5-Chloro-2-(3-chloro-4-fluoro-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
539		(2S)-[5-Bromo-2-(4-trifluoromethyl-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
540		(2S)-[5-Bromo-2-phenylamino-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
541		(2S)-[5-Chloro-2-phenylamino-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

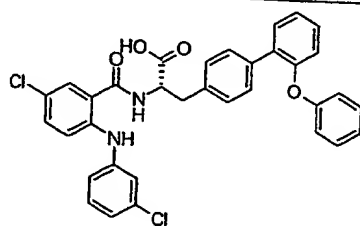
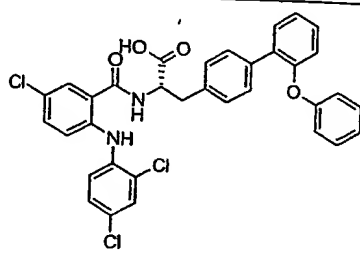
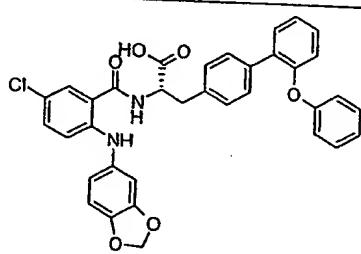
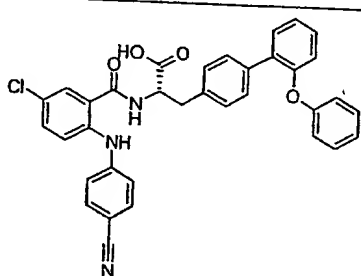
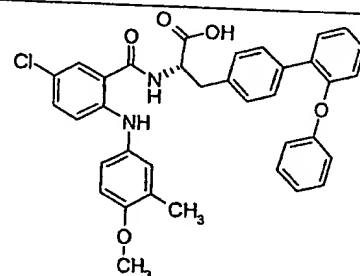


Example	Structure	Name
542		(2S)-[5-Chloro-2-(4-trifluoromethyl-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
543		(2S)-[5-Chloro-2-(3,5-dimethyl-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
544		(2S)-[5-Chloro-2-(3-trifluoromethyl-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
545		(2S)-[5-Chloro-2-(4-methoxy-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
546		(2S)-[2-(4-tert-Butyl-phenylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

Example	Structure	Name
547		(2S)-[5-Chloro-2-(3,4-difluoro-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
548		(2S)-[5-Chloro-2-(4-fluoro-3-methyl-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
549		(2S)-[5-Chloro-2-(3,4-dichloro-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
550		(2S)-[5-Chloro-2-(4-trifluoromethoxy-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
551		(2S)-[5-Chloro-2-(4-methanesulfonyl-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

Example	Structure	Name
552		(2S)-[2-(4-Benzoyloxy-phenylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
553		(2S)-[5-Chloro-2-(naphthalen-1-ylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
554		(2S)-[5-Chloro-2-(naphthalen-2-ylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
555		(2S)-[2-(3,5-Bis-trifluoromethyl-phenylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
556		(2S)-[5-Chloro-2-(4-cyclohexyl-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

Example	Structure	Name
557		(2S)-[2-(Biphenyl-4-ylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
558		(2S)-[2-(3-Butoxy-phenylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
559		(2S)-[5-Chloro-2-(4-ethoxy-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
560		(2S)-[5-Chloro-2-(4-fluoro-3-methoxy-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
561		(2S)-[5-Chloro-2-(4-chloro-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

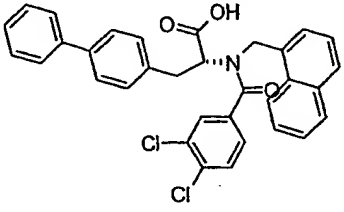
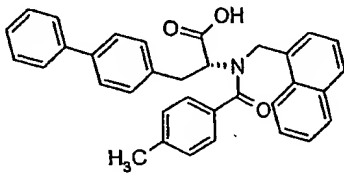
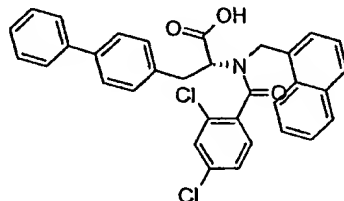
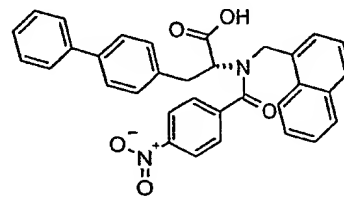
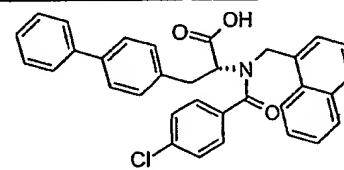
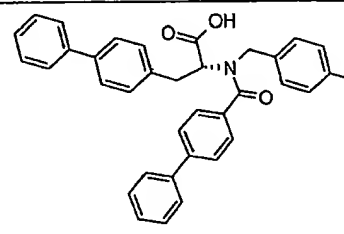
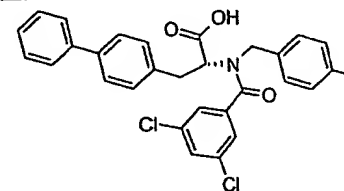
Example	Structure	Name
562		(2S)-[5-Chloro-2-(3-chloro-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
563		(2S)-[5-Chloro-2-(2,4-dichloro-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
564		(2S)-[2-(Benzo[1,3]dioxol-5-ylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
565		(2S)-[5-Chloro-2-(4-cyano-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
566		(2S)-[5-Chloro-2-(4-methoxy-3-methyl-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

Example	Structure	Name
567		(2S)-[5-Chloro-2-(3-isopropyl-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
568		(2S)-[5-Chloro-2-(4-nitro-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
569		(2S)-[5-Chloro-2-(4-methyl-3-nitro-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
570		(2S)-{[(2-Biphenyl-4-yl-methoxycarbonyl-ethyl)-(4'-trifluoromethyl-biphenyl-carbonyl)-amino]-methyl}-(2S)-pyrrolidine-1-carboxylic acid tert-butyl ester
571		(2S)-(2-{[(2-Biphenyl-4-yl-1-methoxycarbonyl-ethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-methyl}-(2S)-pyrrolidine-1-sulfonyl)-benzoic acid methyl ester

Example	Structure	Name
572		3-Biphenyl-4-yl-(2S)-[[(2R)-1-(2-thiophen-2-yl-acetyl)-pyrrolidine-2-methyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
573		(2S)-[[2-(2-Acetylamino-4-methyl-thiazole-5-sulfonylamino)-ethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-3-biphenyl-4-yl-propionic acid methyl ester
574		(2S)-[(Biphenyl-4-carbonyl)-(2-hydroxy-benzyl)-amino]-3-biphenyl-4-yl-propionic acid
575		(2S)-[(Biphenyl-4-carbonyl)-(4-isopropyl-benzyl)-amino]-3-biphenyl-4-yl-propionic acid
576		3-Biphenyl-4-yl-(2S)-[(4-isopropyl-benzyl)-(naphthalene-2-carbonyl)-amino]-propionic acid

Example	Structure	Name
577		3-Biphenyl-4-yl-(2S)-[(4-tert-butyl-benzoyl)-(4-isopropyl-benzyl)amino]-propionic acid
578		3-Biphenyl-4-yl-(2S)-[(3,4-dichloro-benzoyl)-(4-isopropyl-benzyl)amino]-propionic acid
579		(2S)-[(Biphenyl-4-carbonyl)-naphthalen-1-ylmethyl-amino]-3-biphenyl-4-yl-propionic acid
580		3-Biphenyl-4-yl-(2S)-[(naphthalene-2-carbonyl)-naphthalen-1-ylmethyl-amino]-propionic acid
581		3-Biphenyl-4-yl-(2S)-[(4-tert-butyl-benzoyl)-naphthalen-1-ylmethyl-amino]-propionic acid
582		3-Biphenyl-4-yl-(2S)-[(3,5-dichloro-benzoyl)-naphthalen-1-ylmethyl-amino]-propionic acid
583		3-Biphenyl-4-yl-(2S)-[(naphthalene-1-carbonyl)-naphthalen-1-ylmethyl-amino]-propionic acid



Example	Structure	Name
584		3-Biphenyl-4-yl-(2S)-[(3,4-dichloro-benzoyl)-naphthalen-1-ylmethyl-amino]-propionic acid
585		3-Biphenyl-4-yl-(2S)-[(4-methyl-benzoyl)-naphthalen-1-ylmethyl-amino]-propionic acid
586		3-Biphenyl-4-yl-(2S)-[(2,4-dichloro-benzoyl)-naphthalen-1-ylmethyl-amino]-propionic acid
587		3-Biphenyl-4-yl-(2S)-[naphthalen-1-yl-methyl-(4-nitro-benzoyl)-amino]-propionic acid
588		3-Biphenyl-4-yl-(2S)-[(4-chloro-benzoyl)-naphthalen-1-ylmethyl-amino]-propionic acid
589		(2S)-[(Biphenyl-4-carbonyl)-(4-chloro-benzyl)-amino]-3-biphenyl-4-yl-propionic acid
590		3-Biphenyl-4-yl-(2S)-[(4-chloro-benzyl)-(3,5-dichloro-benzoyl)-amino]-propionic acid

Example	Structure	Name
591		(2S)-[(Biphenyl-4-carbonyl)-(5-tert-butyl-2-hydroxy-benzyl)-amino]-3-biphenyl-4-yl-propionic acid
592		Biphenyl-4-carboxylic acid (2S)-[[(biphenyl-4-carbonyl)-(2-biphenyl-4-yl-1-carboxy-ethyl)-amino]-methyl]-4-tert-butyl-phenyl ester
593		3-Biphenyl-4-yl-(2S)-[(4-bromo-benzoyl)-(2-tert-butoxycarbonylamino-ethyl)-amino]-propionic acid
594		3-Biphenyl-4-yl-(2S)-[(2-tert-butoxycarbonylamino-ethyl)-(4'-trifluoromethoxy-biphenyl-4-carbonyl)-amino]-propionic acid
595		(2S)-[(2-Amino-ethyl)-(4-bromo-benzoyl)-amino]-3-biphenyl-4-yl-propionic acid methyl ester

Example	Structure	Name
596		(2S)-[(2-Amino-ethyl)-(4-bromo-benzoyl)-amino]-3-biphenyl-4-yl-propionic acid
597		3-Biphenyl-4-yl-(2S)-[(4-chloro-benzyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
598		(2S)-{2-[(2-Biphenyl-4-yl-1-carboxy-ethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-ethylsulfamoyl}-benzoic acid
599		3-Biphenyl-4-yl-(2S)-[[2-(2-methanesulfonyl-benzenesulfonylamino)-ethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
600		(2S)-{[(2-Biphenyl-4-yl-1-methoxycarbonyl-ethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-methyl}-(2R)-pyrrolidine-1-carboxylic acid tert-butyl ester

Example	Structure	Name
601		(2S)-{2-[(2-Biphenyl-4-yl-1-methoxycarbonyl-ethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-ethylsulfamoyl}-benzoic acid methyl ester
602		3-Biphenyl-4-yl-(2S)-[[2-(2-methanesulfonyl-benzenesulfonylamino)-ethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester
603		3-Biphenyl-4-yl-(2S)-[[2-(4-methanesulfonyl-benzenesulfonylamino)-ethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester
604		3-Biphenyl-4-yl-(2S)-[[1-(2-methanesulfonyl-benzenesulfonyl)-(2S)-pyrrolidin-2-ylmethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester
605		3-Biphenyl-4-yl-(2S)-[[1-(4-methanesulfonyl-benzenesulfonyl)-(2S)-pyrrolidin-2-ylmethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester

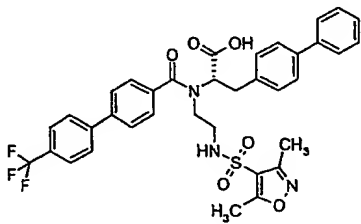
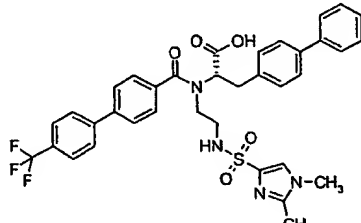
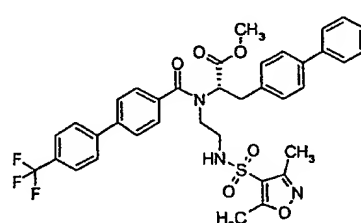
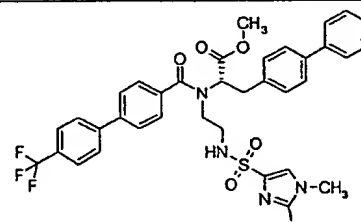
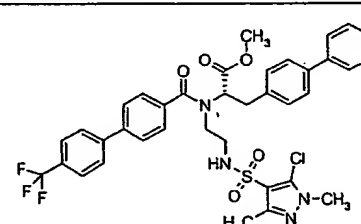
Example	Structure	Name
606		(2S)-[[[(2-Biphenyl-4-yl-1-carboxy-ethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-methyl]-(2S)-pyrrolidine-1-carboxylic acid tert-butyl ester
607		(2S)-[[[(2-Biphenyl-4-yl-1-carboxy-ethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-methyl]-(2R)-pyrrolidine-1-carboxylic acid tert-butyl ester
608		(2S)-(2-[[[(2-Biphenyl-4-yl-1-carboxy-ethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-methyl]-(2S)-pyrrolidine-1-sulfonyl]-benzoic acid methylester
609		3-Biphenyl-4-yl-(2S)-[[1-(2-methanesulfonyl-benzenesulfonyl)-(2S)-pyrrolidin-2-ylmethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
610		3-Biphenyl-4-yl-(2S)-[[1-(4-methanesulfonyl-benzenesulfonyl)-(2S)-pyrrolidin-2-ylmethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid

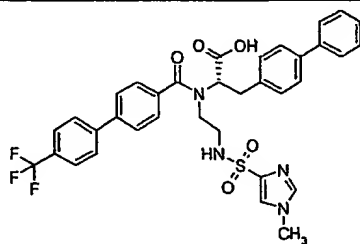
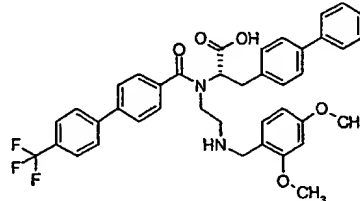
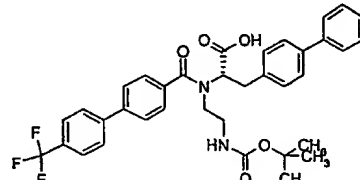
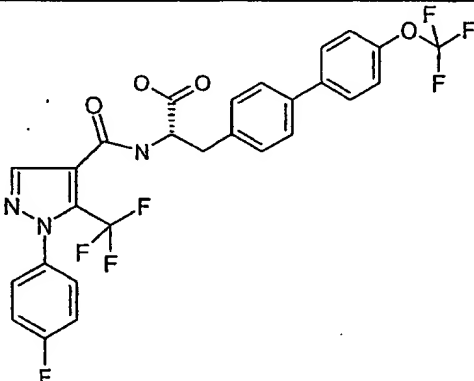
Example	Structure	Name
611		(2S)-2-([(2-Biphenyl-4-yl-1-methoxycarbonyl-ethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-methyl)-(2R)-pyrrolidine-1-sulfonyl-benzoic acid methyl ester
612		3-Biphenyl-4-yl-(2S)-[[1-(2-methanesulfonyl-benzenesulfonyl)-(2R)-pyrrolidin-2-ylmethyl]]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester
613		3-Biphenyl-4-yl-(2S)-[[1-(4-methanesulfonyl-benzenesulfonyl)-(2R)-pyrrolidin-2-ylmethyl]]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester
614		3-Biphenyl-4-yl-(2S)-[[1-(2-thiophen-2-yl-acetyl)-(2R)-pyrrolidin-2-ylmethyl]]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester
615		(2S)-2-([(2-Biphenyl-4-yl-1-carboxy-ethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-methyl)-(2R)-pyrrolidine-1-sulfonyl-benzoic acid methyl ester

Example	Structure	Name
616		3-Biphenyl-4-yl-(2S)-[[1-(2-methanesulfonyl-benzenesulfonyl)-(2R)-pyrrolidin-2-ylmethyl]]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
617		3-Biphenyl-4-yl-(2S)-[(1-cyclopentanecarbonyl-(2S)-pyrrolidin-2-ylmethyl)]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester
618		3-Biphenyl-4-yl-(2S)-[(1-cyclopropanecarbonyl-(2R)-pyrrolidin-2-ylmethyl)]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester
619		3-Biphenyl-4-yl-(2S)-[[1-(4-methanesulfonyl-benzenesulfonyl)-(2R)-pyrrolidin-2-ylmethyl]]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
620		(2S)-[(1-Acetyl-(2S)-pyrrolidin-2-ylmethyl)]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-3-biphenyl-4-yl-propionic acid

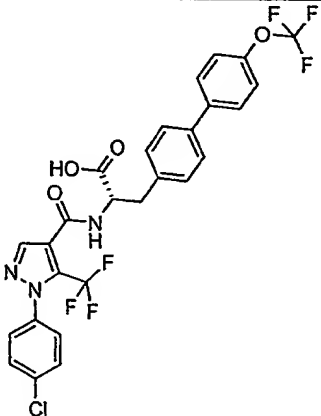
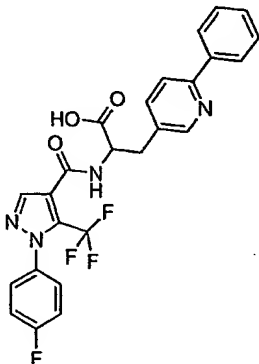
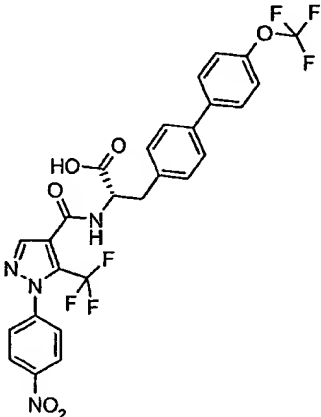
Example	Structure	Name
621		3-Biphenyl-4-yl-(2S)-[[1-(2,2-dimethyl-propionyl)- (2S)-pyrrolidin-2-ylmethyl]- (4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
622		3-Biphenyl-4-yl-(2S)-[[1-(1-cyclopentanecarbonyl-(2S)-pyrrolidin-2-ylmethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
623		(2S)-[[1-(1-Acetyl-(2R)-pyrrolidin-2-ylmethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-3-biphenyl-4-yl-propionic acid
624		3-Biphenyl-4-yl-(2S)-[[1-(1-cyclopropanecarbonyl-(2R)-pyrrolidin-2-ylmethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
625		(2S)-[[2-(2-Acetyl-amino-4-methyl-thiazole-5-sulfonylamino)-ethyl]- (4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-3-biphenyl-4-yl-propionic acid
626		3-Biphenyl-4-yl-(2S)-[[2-(5-chloro-1,3-dimethyl-1H-pyrazole-4-sulfonylamino)-ethyl]- (4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid

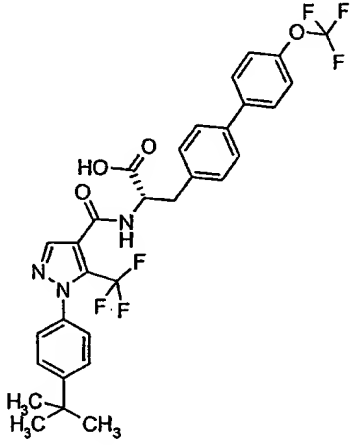
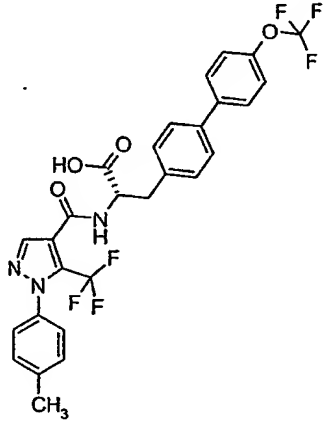
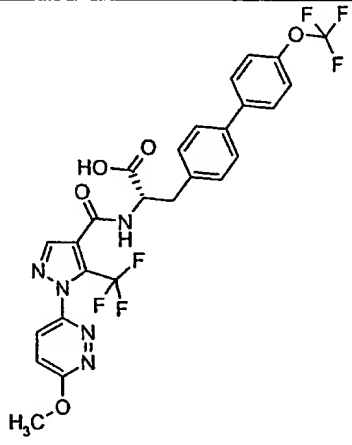


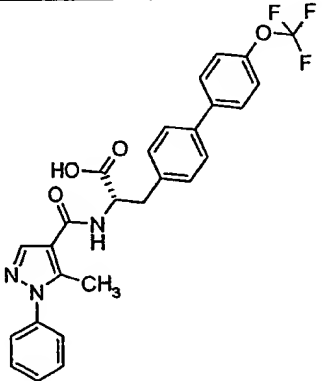
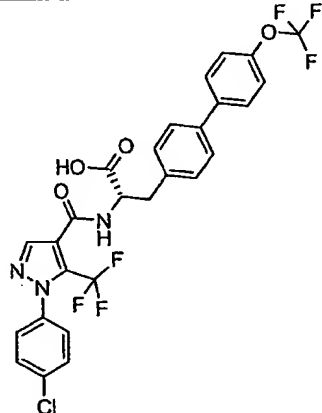
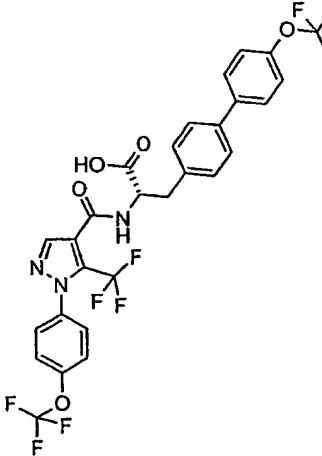
Example	Structure	Name
627		3-Biphenyl-4-yl-(2S)-[[2-(3,5-dimethyl-isoxazole-4-sulfonylamino)-ethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
628		3-Biphenyl-4-yl-(2S)-[[2-(1,2-dimethyl-1H-imidazole-4-sulfonylamino)-ethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
629		3-Biphenyl-4-yl-(2S)-[[2-(3,5-dimethyl-isoxazole-4-sulfonylamino)-ethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester
630		3-Biphenyl-4-yl-(2S)-[[2-(1,2-dimethyl-1H-imidazole-4-sulfonylamino)-ethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester
631		3-Biphenyl-4-yl-(2S)-[[2-(5-chloro-1,3-dimethyl-1H-pyrazole-4-sulfonylamino)-ethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester

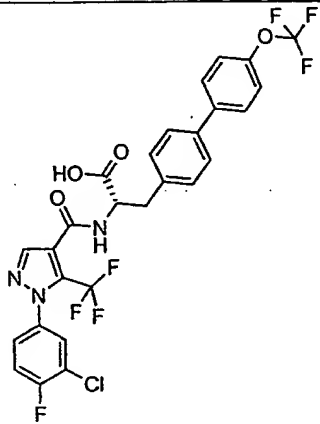
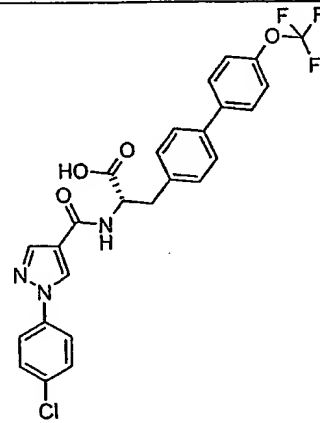
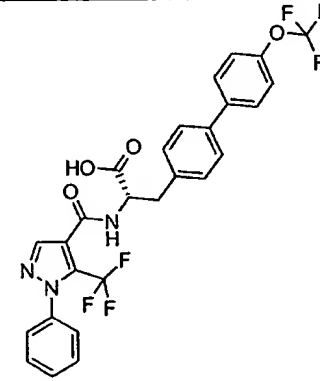
Example	Structure	Name
632		3-Biphenyl-4-yl-(2S)-[[2-(1-methyl-1H-imidazole-4-sulfonylamino)-ethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
633		3-Biphenyl-4-yl-(2S)-[[2-(2,4-dimethoxy-benzylamino)-ethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
634		3-Biphenyl-4-yl-(2S)-[[2-(tert-butoxycarbonylamino-ethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid
635		2-[[1-(4-Fluoro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino]-3-(4'-trifluoromethoxy-biphenyl-4-yl)-propionic acid

Example	Structure	Name
636		2-[[1-(4-Fluoro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino]-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid
637		3-Biphenyl-4-yl-2-[[1-(4-fluoro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino]-propionic acid
638		(2S)-[[1-(4-Chloro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino]-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid
639		3-Biphenyl-4-yl-(2S)-[[1-(4-chloro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino]-propionic acid

Example	Structure	Name
640		(2S)-[[1-(4-Chloro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino]-3-(4'-trifluoromethoxy-biphenyl-4-yl)-propionic acid
641		2-[[1-(4-Fluoro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino]-3-(6-phenyl-pyridin-3-yl)-propionic acid
642		(2S)-[[1-(4-Nitro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino]-3-(4'-trifluoromethoxy-biphenyl-4-yl)-propionic acid

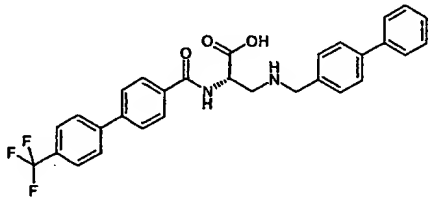
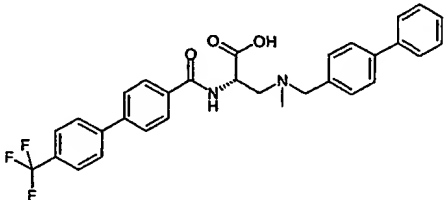
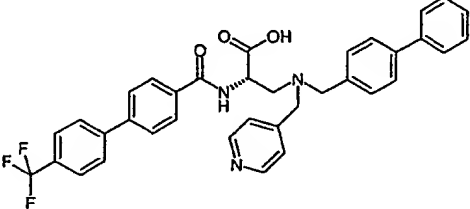
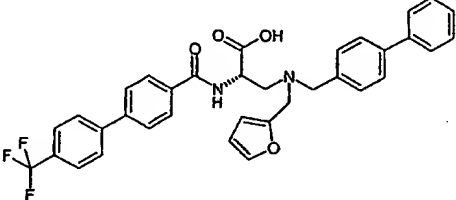
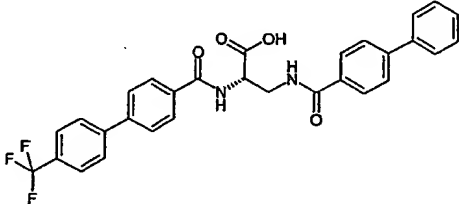
Example	Structure	Name
643		(2S)-[1-(4-tert-Butyl-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino-3-(4'-trifluoromethoxy-biphenyl-4-yl)-propionic acid
644		(2S)-[1-(p-Tolyl-5-trifluoromethyl-1H-pyrazole-4-carbonyl)-amino]-3-(4'-trifluoromethoxy-biphenyl-4-yl)-propionic acid
645		(2S)-[1-(6-Methoxy-pyridazin-3-yl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino-3-(4'-trifluoromethoxy-biphenyl-4-yl)-propionic acid

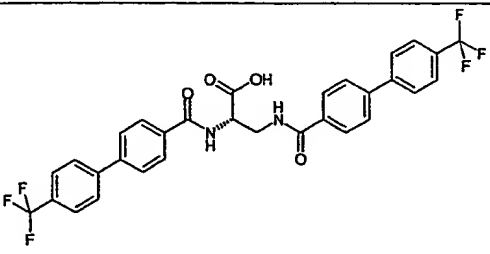
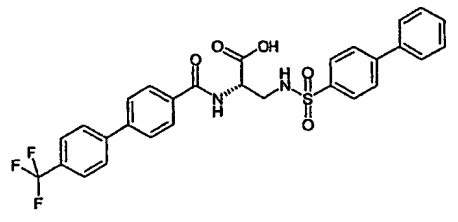
Example	Structure	Name
646		(2S)-[(5-Methyl-1-phenyl-1H-pyrazole-4-carbonyl)-amino]-3-(4'-trifluoromethoxy-biphenyl-4-yl)-propionic acid
647		(2S)-[[1-(4-Chloro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino]-3-(4'-trifluoromethoxy-biphenyl-4-yl)-propionic acid
648		3-(4'-Trifluoromethoxy-biphenyl-4-yl)-(2S)-[[1-(4-trifluoromethoxy-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino]-propionic acid

Example	Structure	Name
649		(2S)-[1-(3-Chloro-4-fluoro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino-3-(4'-trifluoromethoxy-biphenyl-4-yl)-propionic acid
650		(2S)-[1-(4-Chloro-phenyl)-1H-pyrazole-4-carbonyl]-amino-3-(4'-trifluoromethoxy-biphenyl-4-yl)-propionic acid
651		(2S)-[1-Phenyl-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino-3-(4'-trifluoromethoxy-biphenyl-4-yl)-propionic acid

Example	Structure	Name
652		(2S)-[(1-Phenyl-5-trifluoromethyl-1H-pyrazole-4-carbonyl)-amino]-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid
653		3-Biphenyl-4-yl-(2S)-[(1-phenyl-5-trifluoromethyl-1H-pyrazole-4-carbonyl)-amino]-propionic acid
654		(2S)-{[1-(4-Chloro-phenyl)-5-propyl-1H-pyrazole-4-carbonyl]-amino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
655		3-(Biphenyl-4-ylmethoxy)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid



Example	Structure	Name
656		3-[(Biphenyl-4-ylmethyl)-amino]-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid.
657		3-(Biphenyl-4-ylmethyl-methyl-amino)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid:
658		3-(Biphenyl-4-ylmethyl-pyridin-4-ylmethyl-amino)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid:
659		3-(Biphenyl-4-ylmethyl-furan-2-ylmethyl-amino)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid:
660		3-[(Biphenyl-4-carbonyl)-amino]-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid:

Example	Structure	Name
661		(2S), 3-Bis- [(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]- propionic acid:
662		3-(Biphenyl-4-sulfonylamino)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid:

In another aspect, the present invention comprises a pharmaceutical composition comprising the compound of Formula (I) and one or more pharmaceutically acceptable carriers, excipients, or diluents.

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As used herein, the term "lower" refers to a group having between one and six carbons.

As used herein, the term "alkyl" refers to a straight or branched chain hydrocarbon having from one to ten carbon atoms, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, silyloxy optionally substituted by alkoxy, alkyl, or aryl, silyl optionally substituted by alkoxy, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Such an "alkyl" group may contain one or more O, S, S(O), or S(O)<sub>2</sub> atoms. Examples of "alkyl" as used herein include, but are not limited to, methyl, n-butyl, t-butyl, n-pentyl, isobutyl, and isopropyl, and the like.

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As used herein, the term "alkylene" refers to a straight or branched chain divalent hydrocarbon radical having from one to ten carbon atoms, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, silyloxy optionally substituted by alkoxy, alkyl, or aryl, silyl optionally substituted by alkoxy, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Such an "alkylene" group may contain one or more O, S, S(O), or S(O)<sub>2</sub> atoms. Examples of "alkylene" as used herein include, but are not limited to, methylene, ethylene, and the like.

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As used herein, the term "alkenyl" refers to a hydrocarbon radical having from two to ten carbons and at least one carbon-carbon double bond, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, silyloxy optionally substituted by alkoxy, alkyl, or aryl, silyl optionally substituted by alkoxy, alkyl, or aryl, nitro, cyano, halogen, or lower

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perfluoroalkyl, multiple degrees of substitution being allowed. Such an "alkenyl" group may containing one or more O, S, S(O), or S(O)<sub>2</sub> atoms.

As used herein, the term "alkenylene" refers to a straight or branched chain divalent hydrocarbon radical having from two to ten carbon atoms and one or more carbon - carbon double bonds, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, silyloxy optionally substituted by alkoxy, alkyl, or aryl, silyl optionally substituted by alkoxy, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Such an "alkenylene" group may containing one or more O, S, S(O), or S(O)<sub>2</sub> atoms. Examples of "alkenylene" as used herein include, but are not limited to, ethene-1,2-diyl, propene-1,3-diyl, methylene-1,1-diyl, and the like.

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As used herein, the term "alkynyl" refers to a hydrocarbon radical having from two to ten carbons and at least one carbon - carbon triple bond, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, silyloxy optionally substituted by alkoxy, alkyl, or aryl, silyl optionally substituted by alkoxy, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Such an "alkynyl" group may containing one or more O, S, S(O), or S(O)<sub>2</sub> atoms.

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As used herein, the term "alkynylene" refers to a straight or branched chain divalent hydrocarbon radical having from two to ten carbon atoms and one or more carbon - carbon triple bonds, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, silyloxy optionally substituted by alkoxy, alkyl, or aryl, silyl optionally substituted by alkoxy, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Such an "alkynylene" group may containing one or more O, S, S(O), or S(O)<sub>2</sub> atoms. Examples of "alkynylene" as used herein include, but are not limited to, ethyne-1,2-diyl, propyne-1,3-diyl, and the like.

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As used herein, "cycloalkyl" refers to a alicyclic hydrocarbon group optionally possessing one or more degrees of unsaturation, having from three to twelve carbon atoms, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. "Cycloalkyl" includes by way of example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl, and the like.

As used herein, the term "cycloalkylene" refers to an non-aromatic alicyclic divalent hydrocarbon radical having from three to twelve carbon atoms and optionally possessing one or more degrees of unsaturation, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "cycloalkylene" as used herein include, but are not limited to, cyclopropyl-1,1-diyl, cyclopropyl-1,2-diyl, cyclobutyl-1,2-diyl, cyclopentyl-1,3-diyl, cyclohexyl-1,4-diyl, cycloheptyl-1,4-diyl, or cyclooctyl-1,5-diyl, and the like.

As used herein, the term "heterocyclic" or the term "heterocyclyl" refers to a three to twelve-membered heterocyclic ring optionally possessing one or more degrees of unsaturation, containing one or more heteroatomic substitutions selected from S, SO, SO<sub>2</sub>, O, or N, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Such a ring may be optionally fused to one or more of another "heterocyclic" ring(s) or cycloalkyl ring(s). Examples of "heterocyclic" include, but are not limited to, tetrahydrofuran, 1,4-dioxane, 1,3-dioxane, piperidine, pyrrolidine, morpholine, piperazine, and the like.

As used herein, the term "heterocyclylene" refers to a three to twelve-membered heterocyclic ring diradical optionally having one or more degrees of unsaturation containing one or more heteroatoms selected from S, SO, SO<sub>2</sub>, O, or N, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower

alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Such a ring may be optionally fused to one or more benzene rings or to one or more of another "heterocyclic" rings or cycloalkyl rings. Examples of "heterocyclylene" include, but are not limited to, tetrahydrofuran-2,5-diyl, morpholine-2,3-diyl, pyran-2,4-diyl, 1,4-dioxane-2,3-diyl, 1,3-dioxane-2,4-diyl, piperidine-2,4-diyl, piperidine-1,4-diyl, pyrrolidine-1,3-diyl, morpholine-2,4-diyl, piperazine-1,4-diyl, and the like.

As used herein, the term "aryl" refers to a benzene ring or to an optionally substituted benzene ring system fused to one or more optionally substituted benzene rings, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, di(lower alkyl)aminoalkyl, aminoalkyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acylamino, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, silyloxy optionally substituted by alkoxy, alkyl, or aryl, silyl optionally substituted by alkoxy, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Examples of aryl include, but are not limited to, phenyl, 2-naphthyl, 1-naphthyl, 1-anthracenyl, and the like.

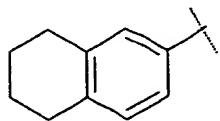
As used herein, the term "arylene" refers to a benzene ring diradical or to a benzene ring system diradical fused to one or more optionally substituted benzene rings, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, di(lower alkyl)aminoalkyl, aminoalkyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acylamino, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, silyloxy optionally substituted by alkoxy, alkyl, or aryl, silyl optionally substituted by alkoxy, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "arylene" include, but are not limited to, benzene-1,4-diyl, naphthalene-1,8-diyl, and the like.

As used herein, the term "heteroaryl" refers to a five - to seven - membered aromatic ring, or to a polycyclic heterocyclic aromatic ring, containing one or more nitrogen, oxygen, or sulfur heteroatoms, where N-oxides and sulfur monoxides and sulfur dioxides are

permissible heteroaromatic substitutions, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, silyloxy optionally substituted by alkoxy, alkyl, or aryl, silyl optionally substituted by alkoxy, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. For polycyclic aromatic ring systems, one or more of the rings may contain one or more heteroatoms. Examples of "heteroaryl" used herein are furan, thiophene, pyrrole, imidazole, pyrazole, triazole, tetrazole, thiazole, oxazole, isoxazole, oxadiazole, thiadiazole, isothiazole, pyridine, pyridazine, pyrazine, pyrimidine, quinoline, isoquinoline, quinazoline, benzofuran, benzothiophene, indole, and indazole, and the like.

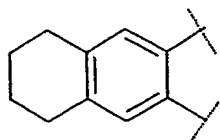
As used herein, the term "heteroarylene" refers to a five - to seven - membered aromatic ring diradical, or to a polycyclic heterocyclic aromatic ring diradical, containing one or more nitrogen, oxygen, or sulfur heteroatoms, where N-oxides and sulfur monoxides and sulfur dioxides are permissible heteroaromatic substitutions, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, silyloxy optionally substituted by alkoxy, alkyl, or aryl, silyl optionally substituted by alkoxy, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. For polycyclic aromatic ring system diradicals, one or more of the rings may contain one or more heteroatoms. Examples of "heteroarylene" used herein are furan-2,5-diyl, thiophene-2,4-diyl, 1,3,4-oxadiazole-2,5-diyl, 1,3,4-thiadiazole-2,5-diyl, 1,3-thiazole-2,4-diyl, 1,3-thiazole-2,5-diyl, pyridine-2,4-diyl, pyridine-2,3-diyl, pyridine-2,5-diyl, pyrimidine-2,4-diyl, quinoline-2,3-diyl, and the like.

As used herein, the term "fused cycloalkylaryl" refers to a cycloalkyl group fused to an aryl group, the two having two atoms in common, and wherein the aryl group is the point of substitution. Examples of "fused cycloalkylaryl" used herein include 5-indanyl, 5,6,7,8-tetrahydro-2-naphthyl,



, and the like.

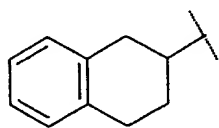
As used herein, the term "fused cycloalkylarylene" refers to a fused cycloalkylaryl, wherein the aryl group is divalent. Examples include



, and the like.

5

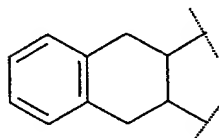
As used herein, the term "fused arylcycloalkyl" refers to an aryl group fused to a cycloalkyl group, the two having two atoms in common, and wherein the cycloalkyl group is the point of substitution. Examples of "fused arylcycloalkyl" used herein include 1-indanyl, 2-indanyl, 1-(1,2,3,4-tetrahydronaphthyl),



, and the like.

10

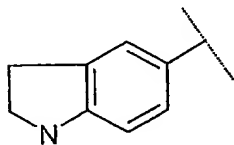
As used herein, the term "fused arylcycloalkylene" refers to a fused arylcycloalkyl, wherein the cycloalkyl group is divalent. Examples include



, and the like.

15

As used herein, the term "fused heterocyclaryl" refers to a heterocyclaryl group fused to an aryl group, the two having two atoms in common, and wherein the aryl group is the point of substitution. Examples of "fused heterocyclaryl" used herein include 3,4-methylenedioxy-1-phenyl,

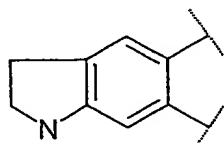


, and the like

20

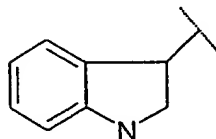


As used herein, the term "fused heterocyclaryl" refers to a fused heterocyclaryl, wherein the aryl group is divalent. Examples include



, and the like.

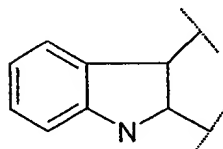
- 5 As used herein, the term "fused arylheterocycl" refers to an aryl group fused to a heterocycl group, the two having two atoms in common, and wherein the heterocycl group is the point of substitution. Examples of "fused arylheterocycl" used herein include 2-(1,3-benzodioxolyl),



, and the like.

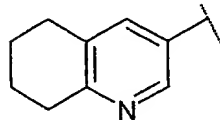
10

As used herein, the term "fused arylheterocyclene" refers to a fused arylheterocycl, wherein the heterocycl group is divalent. Examples include



, and the like.

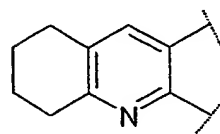
- 15 As used herein, the term "fused cycloalkylheteroaryl" refers to a cycloalkyl group fused to a heteroaryl group, the two having two atoms in common, and wherein the heteroaryl group is the point of substitution. Examples of "fused cycloalkylheteroaryl" used herein include 5-aza-6-indanyl,



, and the like.

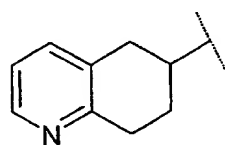
20

As used herein, the term "fused cycloalkylheteroarylene" refers to a fused cycloalkylheteroaryl, wherein the heteroaryl group is divalent. Examples include



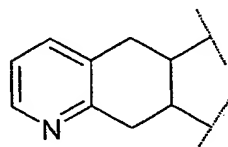
, and the like.

As used herein, the term "fused heteroarylcycloalkyl" refers to a heteroaryl group fused to a cycloalkyl group, the two having two atoms in common, and wherein the cycloalkyl group is the point of substitution. Examples of "fused heteroarylcycloalkyl" used herein  
5 include 5-aza-1-indanyl,



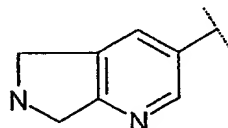
and the like.

As used herein, the term "fused heteroarylcycloalkylene" refers to a fused heteroarylcycloalkyl, wherein the cycloalkyl group is divalent. Examples include



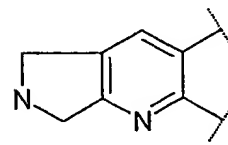
10 , and the like.

As used herein, the term "fused heterocyclylheteroaryl" refers to a heterocyclyl group fused to a heteroaryl group, the two having two atoms in common, and wherein the heteroaryl group is the point of substitution. Examples of "fused heterocyclylheteroaryl" used herein include 1,2,3,4-tetrahydro-beta-carbolin-8-yl,



and the like.

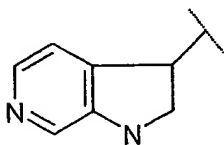
As used herein, the term "fused heterocyclylheteroarylene" refers to a fused heterocyclylheteroaryl, wherein the heteroaryl group is divalent. Examples include



20 , and the like.

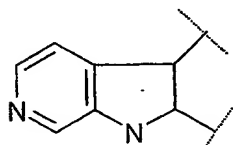
As used herein, the term "fused heteroarylheterocyclyl" refers to a heteroaryl group fused to a heterocyclyl group, the two having two atoms in common, and wherein the heterocyclyl group is the point of substitution. Examples of "fused heteroarylheterocyclyl"

used herein include -5-aza-2,3-dihydrobenzofuran-2-yl,



, and the like.

As used herein, the term "fused heteroarylheterocyclene" refers to a fused  
5 heteroarylheterocycl, wherein the heterocycl group is divalent. Examples include



, and the like.

As used herein, the term "acid isostere" refers to a substituent group which will ionize  
at physiological pH to bear a net negative charge. Examples of such "acid isosteres" include  
10 but are not limited to heteroaryl groups such as but not limited to isoxazol-3-ol-5-yl, 1H-  
tetrazole-5-yl, or 2H-tetrazole-5-yl. Such acid isosteres include but are not limited to  
heterocycl groups such as but not limited to imidazolidine-2,4-dione-5-yl, imidazolidine-2,4-  
dione-1-yl, 1,3-thiazolidine-2,4-dione-5-yl, or 5-hydroxy-4H-pyran-4-on-2-yl.

15 As used herein, the term "direct bond", where part of a structural variable  
specification, refers to the direct joining of the substituents flanking (preceding and  
succeeding) the variable taken as a "direct bond".

As used herein, the term "alkoxy" refers to the group  $R_aO-$ , where  $R_a$  is alkyl.  
20

As used herein, the term "alkenyloxy" refers to the group  $R_aO-$ , where  $R_a$  is alkenyl.

As used herein, the term "alkynyloxy" refers to the group  $R_aO-$ , where  $R_a$  is alkynyl.

25 As used herein, the term "alkylsulfanyl" refers to the group  $R_aS-$ , where  $R_a$  is alkyl.

As used herein, the term "alkenylsulfanyl" refers to the group  $R_aS-$ , where  $R_a$  is  
alkenyl.

30 As used herein, the term "alkynylsulfanyl" refers to the group  $R_aS-$ , where  $R_a$  is  
alkynyl.

As used herein, the term "alkylsulfenyl" refers to the group  $R_aS(O)-$ , where  $R_a$  is alkyl.

5 As used herein, the term "alkenylsulfenyl" refers to the group  $R_aS(O)-$ , where  $R_a$  is alkenyl.

As used herein, the term "alkynylsulfenyl" refers to the group  $R_aS(O)-$ , where  $R_a$  is alkynyl.

10 As used herein, the term "alkylsulfonyl" refers to the group  $R_aSO_2-$ , where  $R_a$  is alkyl.

As used herein, the term "alkenylsulfonyl" refers to the group  $R_aSO_2-$ , where  $R_a$  is alkenyl.

15 As used herein, the term "alkynylsulfonyl" refers to the group  $R_aSO_2-$ , where  $R_a$  is alkynyl.

As used herein, the term "acyl" refers to the group  $R_aC(O)-$ , where  $R_a$  is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, or heterocyclyl.

20 As used herein, the term "aroyl" refers to the group  $R_aC(O)-$ , where  $R_a$  is aryl.

As used herein, the term "heteroaroyl" refers to the group  $R_aC(O)-$ , where  $R_a$  is heteroaryl.

25 As used herein, the term "alkoxycarbonyl" refers to the group  $R_aOC(O)-$ , where  $R_a$  is alkyl.

30 As used herein, the term "acyloxy" refers to the group  $R_aC(O)O-$ , where  $R_a$  is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, or heterocyclyl.

As used herein, the term "aroyloxy" refers to the group  $R_aC(O)O-$ , where  $R_a$  is aryl.

35 As used herein, the term "heteroaroyloxy" refers to the group  $R_aC(O)O-$ , where  $R_a$  is heteroaryl.

As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s) which occur and events that do not occur.

5 As used herein, the term "substituted" refers to substitution with the named substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated.

10 As used herein, the terms "contain" or "containing" can refer to in-line substitutions at any position along the above defined alkyl, alkenyl, alkynyl or cycloalkyl substituents with one or more of any of O, S, SO, SO<sub>2</sub>, N, or N-alkyl, including, for example, -CH<sub>2</sub>-O-CH<sub>2</sub>-, -CH<sub>2</sub>-SO<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-NH-CH<sub>3</sub> and so forth.

15 Whenever the terms "alkyl" or "aryl" or either of their prefix roots appear in a name of a substituent (e.g. arylalkoxyaryloxy) they shall be interpreted as including those limitations given above for "alkyl" and "aryl". Alkyl or cycloalkyl substituents shall be recognized as being functionally equivalent to those having one or more degrees of unsaturation. Designated numbers of carbon atoms (e.g. C<sub>1-10</sub>) shall refer independently to the number of carbon atoms in an alkyl, alkenyl or alkynyl or cyclic alkyl moiety or to the alkyl portion of a  
20 larger substituent in which the term "alkyl" appears as its prefix root.

As used herein, the term "oxo" shall refer to the substituent =O.

25 As used herein, the term "halogen" or "halo" shall include iodine, bromine, chlorine and fluorine.

As used herein, the term "mercapto" shall refer to the substituent -SH.

30 As used herein, the term "carboxy" shall refer to the substituent -COOH.

As used herein, the term "cyano" shall refer to the substituent -CN.

As used herein, the term "aminosulfonyl" shall refer to the substituent -SO<sub>2</sub>NH<sub>2</sub>.

35 As used herein, the term "carbamoyl" shall refer to the substituent -C(O)NH<sub>2</sub>.

As used herein, the term "sulfanyl" shall refer to the substituent -S-.

As used herein, the term "sulfenyl" shall refer to the substituent -S(O)-.

As used herein, the term "sulfonyl" shall refer to the substituent -S(O)<sub>2</sub>-.

5

The compounds can be prepared readily according to the following reaction Schemes (in which variables are as defined before or are defined) using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail.

10

The present invention also provides a method for the synthesis of compounds useful as intermediates in the preparation of compounds of Formula (I) along with methods for the preparation of compounds of Formula (I).

15

Scheme I describes the synthesis of an intermediate of structure (4).

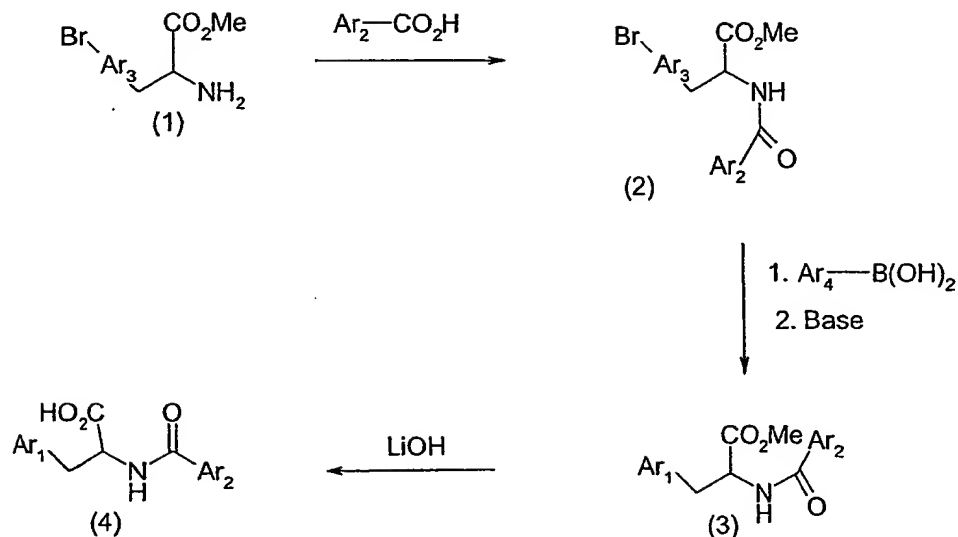
Ar<sub>3</sub> and Ar<sub>4</sub> are, independently, groups such as, but not limited to, a heteroaryl, heteroarylene, arylene, or aryl ring system.

20

As shown in Scheme I, in one embodiment, bromo- or iodo- substituted aryl alanine methyl ester (or amino acid esterified in linkage to Wang resin) (1) is treated with a carboxylic acid in the presence of a coupling reagent, such as, but not limited to, diisopropyl carbodiimide (DIC) to form the amide (2). The resulting amide is then subjected to coupling with an arylboronic acid in the presence of a catalyst such as but not limited to tetrakis(triphenylphosphine)palladium (0), in the presence of base such as, but not limited to, sodium carbonate to form compound (3). The methyl ester (3) is hydrolyzed using a base such as, but not limited to, LiOH to provide the free carboxylic acid (4), where Ar<sub>1</sub> and Ar<sub>2</sub> are as defined for Formula (I).

25  
30

Scheme I



5 Scheme II describes the preparation of a compound of structure (4).

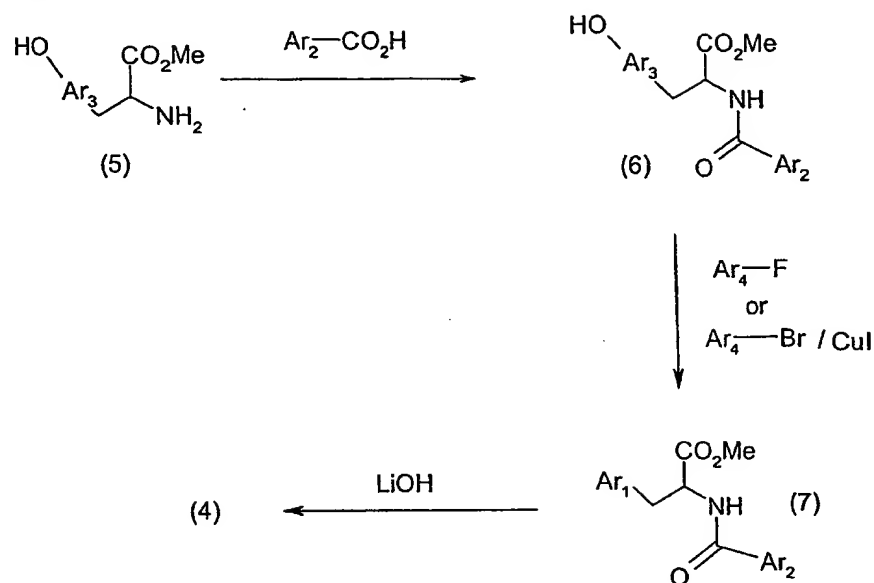
$\text{Ar}_3$  and  $\text{Ar}_4$  are, independently, groups such as but not limited to a heteroaryl, heteroarylene, arylene, or aryl ring system.

10 As shown in Scheme II, in another embodiment, an aryl hydroxy amino acid methyl ester (or amino acid esterified in linkage to Wang resin) (5) is treated with a carboxylic acid  $\text{Ar}_2-\text{CO}_2\text{H}$  in the presence of a coupling reagent such as, but not limited to, diisopropyl carbodiimide (DIC) to form the amide (6). The resulting amide is then subjected to:

15 nucleophilic substitutions with an optionally substituted electron –deficient fluoroaromatic or fluoroheteroaromatic in the presence of base such as, but not limited to, potassium carbonate; or 2) coupling with an aryl bromide, or heteroaryl bromide, and copper iodide in the presence of a base including, but not limited to, cesium carbonate to form compound (7). The methyl ester in (7) is hydrolyzed using a base such as  $\text{LiOH}$  to provide the free carboxylic acid (4), where  $\text{Ar}_1$  and  $\text{Ar}_2$  are as defined for Formula (I)

20

Scheme II



Scheme III describes the preparation of a compound of formula (4).

- 5             $\text{Ar}_5$  and  $\text{Ar}_6$  are, independently, groups such as but not limited to a heteroaryl, heteroarylene, arylene, or aryl ring system.

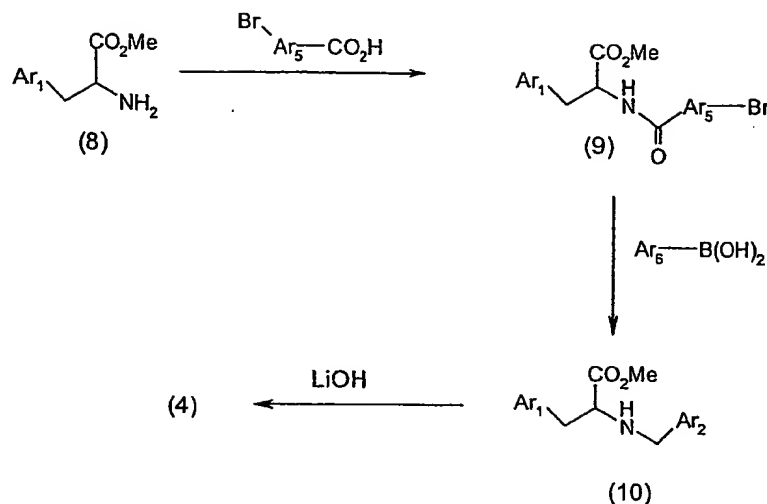
As shown in Scheme III, in another embodiment, an amino acid methyl ester (or, alternately, an amino acid esterified in linkage to Wang resin) (8) is treated with a bromo-

10 substituted aryl carboxylic acid in the presence of a coupling reagent such as, but not limited to, diisopropyl carbodiimide (DIC) to form the amide (9). The resulting amide then is subjected to coupling with an arylboronic acid or heteroarylboronic acid in the presence of a catalyst such as but not limited to tetrakis(triphenylphosphine)palladium(0), in the presence of base such as, but not limited to, sodium carbonate to form compound (10). The methyl

15 ester (10) is hydrolyzed using a base such as, but not limited to,  $\text{LiOH}$  to provide the free carboxylic acid (4), where  $\text{Ar}_1$  and  $\text{Ar}_2$  are as defined for Formula (I)



Scheme III



Scheme IV describes the synthesis of a compound of formula (4).

5

$\text{Ar}_3$ ,  $\text{Ar}_7$ ,  $\text{Ar}_5$  and  $\text{Ar}_6$  are, independently, groups such as but not limited to a heteroaryl, heteroarylene, arylene, or aryl ring system.

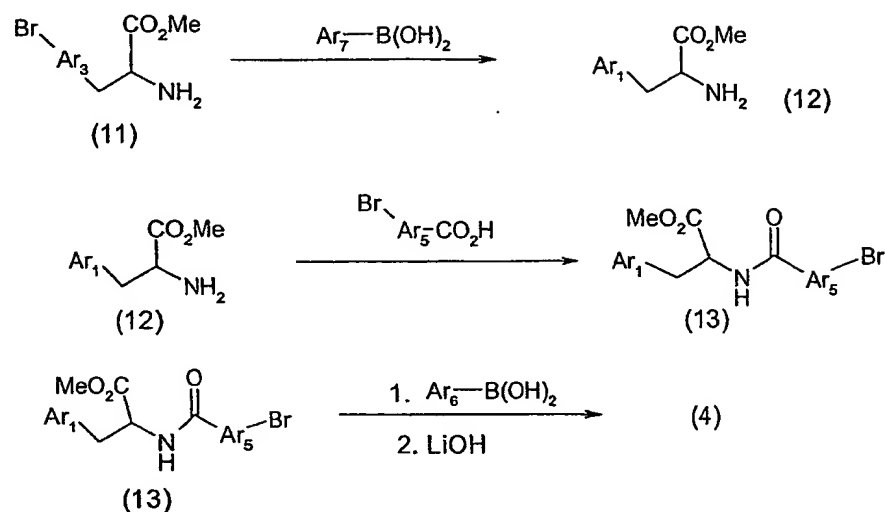
As shown in Scheme IV, in another embodiment, a bromo or iodo aryl alanine methyl ester (or amino acid esterified in linkage to Wang resin) (11) is subjected to coupling with an arylboronic acid in the presence of a catalyst such as but not limited to tetrakis(triphenylphosphine)palladium(0), in the presence of base such as but not limited to sodium carbonate to form compound (12). The resulting compound is treated with a bromo- or iodo-substituted aryl carboxylic acid in the presence of a coupling reagent such as, but not limited to, diisopropyl carbodiimide (DIC) to form the amide (13). The resulting amide is then subjected to coupling with an arylboronic acid or heteroarylboronic acid in the presence of a catalyst such as but not limited to tetrakis(triphenylphosphine)palladium(0), in the presence of base such as, but not limited to, sodium carbonate, and the product methyl ester is hydrolyzed using a base such as  $\text{LiOH}$  to provide the free carboxylic acid (4), where  $\text{Ar}_1$  and  $\text{Ar}_2$  are as defined for Formula (I).

10

15

20

Scheme IV



Scheme V describes the preparation of a compound of formula (16).

5

$\text{Ar}_3$  and  $\text{Ar}_7$  are, independently, groups such as but not limited to a heteroaryl, heteroarylene, arylene, or aryl ring system.

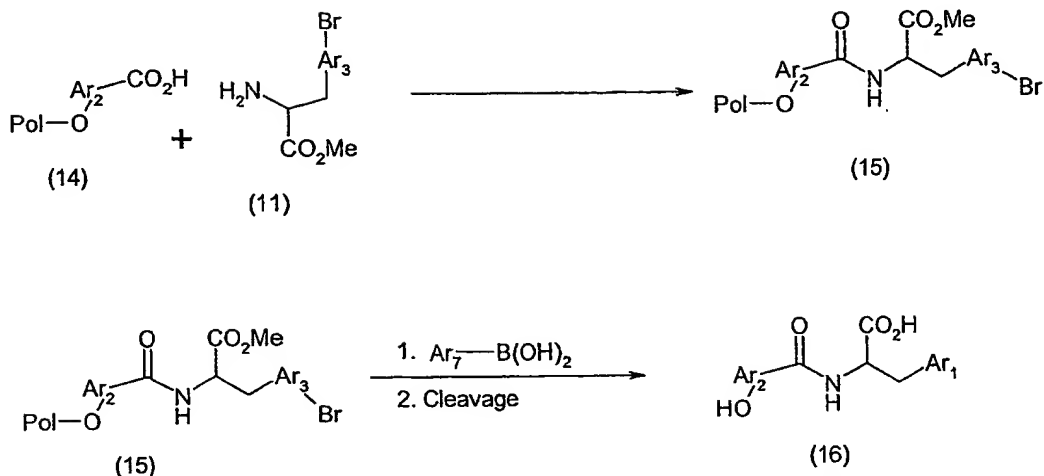
Pol is a functionalized polymeric support, such as but not limited to Wang Resin.

10

As shown in Scheme V, in another embodiment, a hydroxy aryl ester loaded onto the Wang Bromo resin or Merrifield resin using base such as, but not limited to, sodium methoxide in DMA, and hydrolyzed to give (14), is coupled with a bromo- or iodo-substituted aryl amino acid methyl ester (11) in the presence of a coupling reagent such as, but not limited to, diisopropyl carbodiimide (DIC) to give the amide (15). The resulting amide (15) is then subjected to a coupling with an arylboronic acid or heteroarylboronic acid in the presence of a catalyst such as but not limited to tetrakis(triphenylphosphine)palladium(0), in the presence of base such as, but not limited to, sodium carbonate followed by cleavage from the resin with  $\text{TMSBr/TFA/DCM}$  (1:1:1) or a similar suitable cleavage cocktail to yield the desired product (16), where  $\text{Ar}_1$  and  $\text{Ar}_2$  are as defined for Formula (I)

20

Scheme V



Scheme VI describes the preparation of a compound of formula (19).

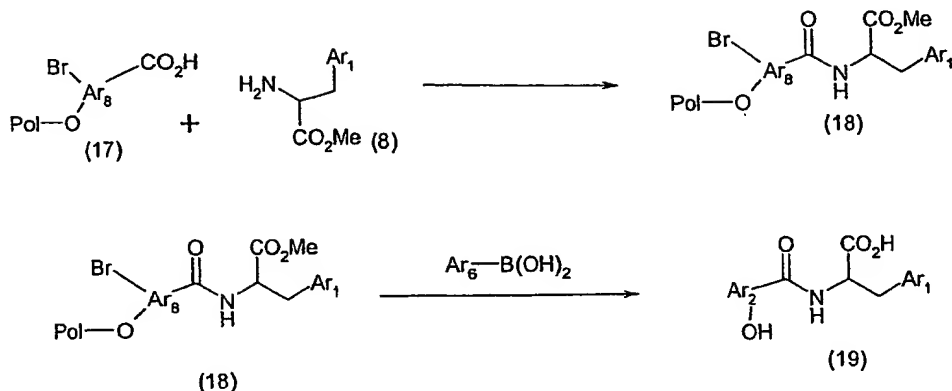
- 5           Ar<sub>6</sub> and Ar<sub>8</sub> are, independently, groups such as but not limited to a heteroaryl, heteroarylene, arylene, or aryl ring system.

Pol is a functionalized polymeric support, such as but not limited to Wang Resin.

- 10           As shown in Scheme VI, in another embodiment, a hydroxy aryl ester loaded onto the Wang Bromo resin, Merrifield resin, or other suitable support using base such as, but not limited to, sodium methoxide in DMA, is hydrolyzed to give (17), and is coupled with an amino acid methyl ester (8) in the presence of a coupling reagent such as, but not limited to, diisopropyl carbodiimide (DIC) to give the amide (18). The resulting amide (18) is then
- 15           subjected to a coupling with an arylboronic acid or heteroarylboronic acid in the presence of a catalyst such as but not limited to tetrakis(triphenylphosphine)palladium(0), in the presence of base such as, but not limited to, sodium carbonate, and is then cleaved from the resin with TMSBr/TFA/DCM (1:1:1) or a similar suitable cleavage cocktail to yield the desired product (19), where Ar<sub>1</sub> and Ar<sub>2</sub> are as defined for Formula (I).

20

Scheme VI



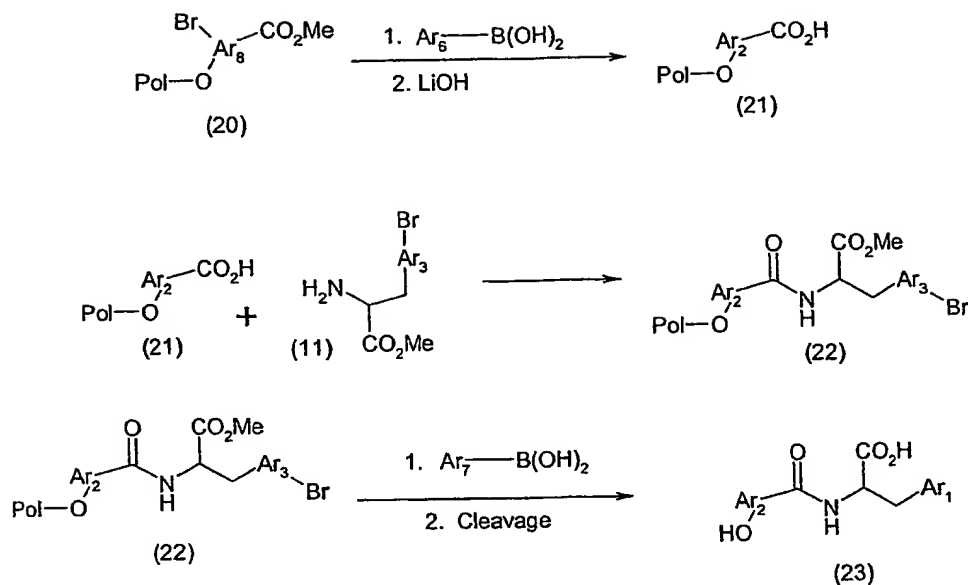
5 Scheme VII describes the synthesis of a compound of formula (23).

Ar<sub>3</sub>, Ar<sub>7</sub>, and Ar<sub>6</sub> are, independently, groups such as but not limited to a heteroaryl, heteroarylene, arylene, or aryl ring system.

10 Pol is a functionalized polymeric support, such as but not limited to Wang Resin.

As shown in Scheme VII, in another embodiment, a bromo hydroxy aryl ester (20) loaded onto Wang Bromo resin, Merrifield resin, or other suitable support using base such as, but not limited to, sodium methoxide in DMF, is then subjected to a coupling with an  
 15 arylboronic acid or heteroarylboronic acid in the presence of a catalyst such as but not limited to tetrakis(triphenylphosphine)palladium(0), in the presence of base such as, but not limited to, sodium carbonate, followed by hydrolysis of the product ester to yield the acid (21). The resulting carboxylic acid (21) is then subjected to coupling with a bromo- or iodo-substituted aryl amino acid methyl ester (11) in the presence of a coupling reagent such as,  
 20 but not limited to, diisopropyl carbodiimide (DIC) to give the amide (22). The resulting amide (22) is then subjected to a coupling with an arylboronic acid or heteroaryl boronic acid in the presence of a catalyst such as but not limited to tetrakis(triphenylphosphine)palladium(0), in the presence of base such as, but not limited to, sodium carbonate followed by cleavage from the resin with TMSBr/TFA/DCM (1:1:1) or a similar cleavage cocktail to yield the  
 25 desired product (23), where Ar<sub>1</sub> and Ar<sub>2</sub> are as defined for Formula (I).

Scheme VII



5

Scheme VIII describes the preparation of a compound of formula (29).

$\text{Ar}_7$ ,  $\text{Ar}_9$ ,  $\text{Ar}_{10}$ , and  $\text{Ar}_{11}$  are, independently, groups such as but not limited to a heteroaryl, heteroarylene, arylene, or aryl ring system.

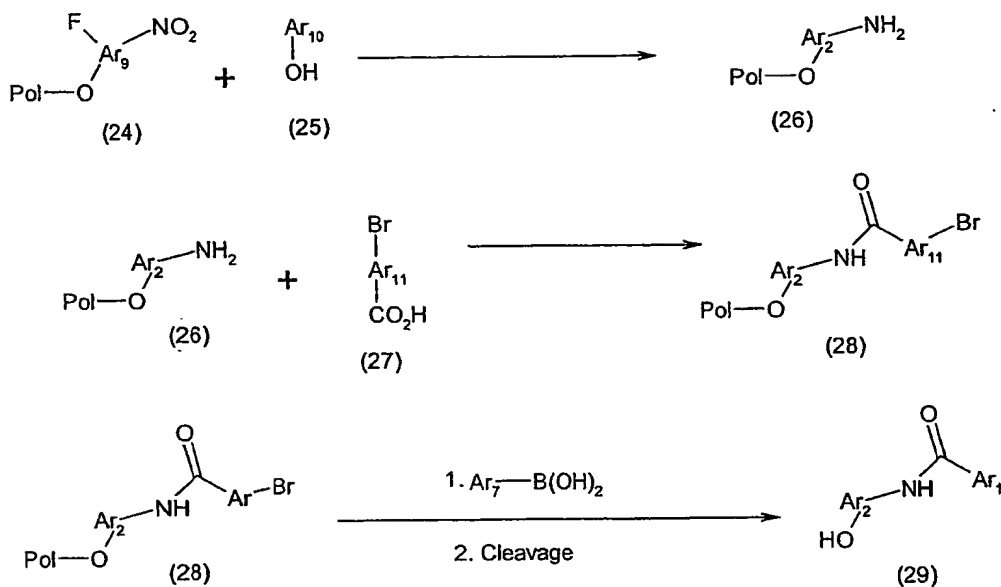
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As shown in Scheme VIII, in another embodiment, a fluoro nitro phenol (24) loaded onto a polymer such as Wang Bromo resin using base such as, but not limited to, sodium methoxide in DMA, is then treated with a hydroxy aryl compound (25) in the presence of base, followed by reduction of the nitro group to give the free amine (26). The resulting amine (26) is then subjected to coupling with a bromo- or iodo-substituted aryl acid (27) in the presence of a coupling reagent such as, but not limited to, diisopropyl carbodiimide (DIC) to give the amide (28). The resulting amide (28) is then subjected to a coupling with an arylboronic acid or heteroarylboronic acid in the presence of a catalyst such as but not limited to tetrakis(triphenylphosphine)palladium(0), in the presence of base such as, but not limited to, sodium carbonate followed by cleavage from the resin with  $\text{TMSBr/TFA/DCM}$  (1:1:1) or a similar suitable cleavage cocktail to yield the desired product (29), where  $\text{Ar}_1$  and  $\text{Ar}_2$  are as defined for Formula (I).

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20

Scheme VIII



Scheme IX describes the preparation of a compound of formula (32).

5

Ar<sub>6</sub>, Ar<sub>12</sub>, and Ar<sub>13</sub> are, independently, groups such as but not limited to a heteroaryl, heteroarylene, arylene, or aryl ring system.

PG<sub>1</sub> is an amino protecting group such as allyloxycarbonyl or tert-butoxycarbonyl.

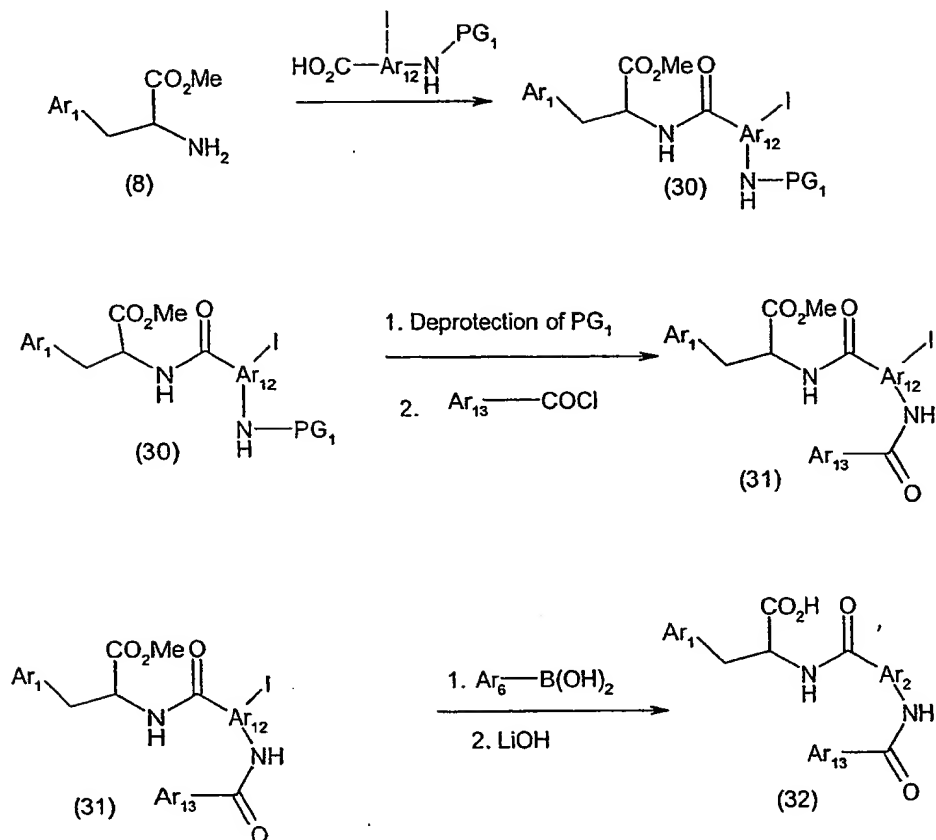
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As shown in Scheme IX, In another embodiment, an aryl amino acid methyl ester (8) is reacted with an iodo-substituted aryl amino carboxylic acid (the amino group of which may be protected with an amino protecting group PG<sub>1</sub>) in the presence of a coupling reagent such as, but not limited to, diisopropyl carbodiimide (DIC) giving the amide (30). The amino group of the amide (30) may be then deprotected, if desired, by treatment with, in the case of PG<sub>1</sub> as tert-butoxycarbonyl, TFA, and is then treated with an aroyl chloride in the presence of a base such as pyridine or TEA to give the iodo amide (31). The amide (31) is subjected to coupling with an arylboronic acid or heteroaryl boronic acid in the presence of a catalyst such as but not limited to tetrakis(triphenylphosphine)palladium(0), in the presence of base such as, but not limited to, sodium carbonate. Hydrolysis of the product methyl ester with an alkaline reagent such as LiOH provides compound (32), where Ar<sub>1</sub> and Ar<sub>2</sub> are as defined for Formula (I).

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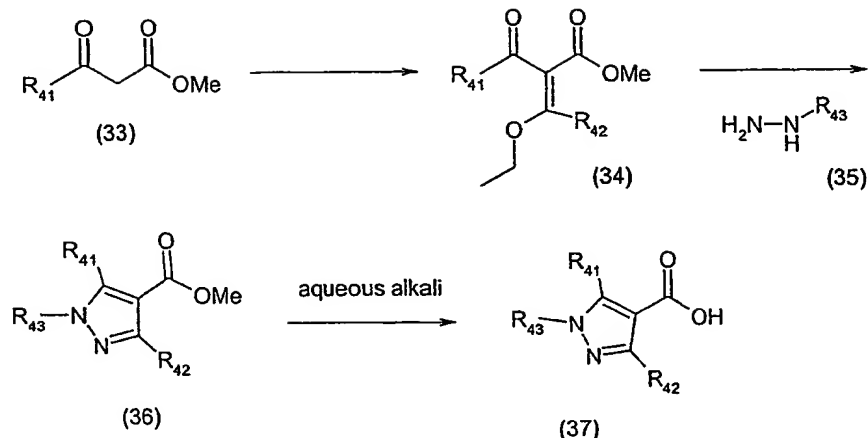
Scheme IX



In Scheme X, in another embodiment, a beta ketoester (33) may be treated with a reagent such as triethyl orthoformate or triethyl orthoacetate in the presence of acetic anhydride and heat to afford the ethoxy olefin derivative (34).  $\text{R}_4$  is a group such as but not limited to aryl, heteroaryl, or alkyl. The derivative (34) may be treated with a hydrazine derivative (35) to afford the pyrazole (36). Hydrolysis of the ester of (36) with aqueous alkali and mild acidification with a weak acid such as aqueous citric acid affords (37).

10

Scheme X

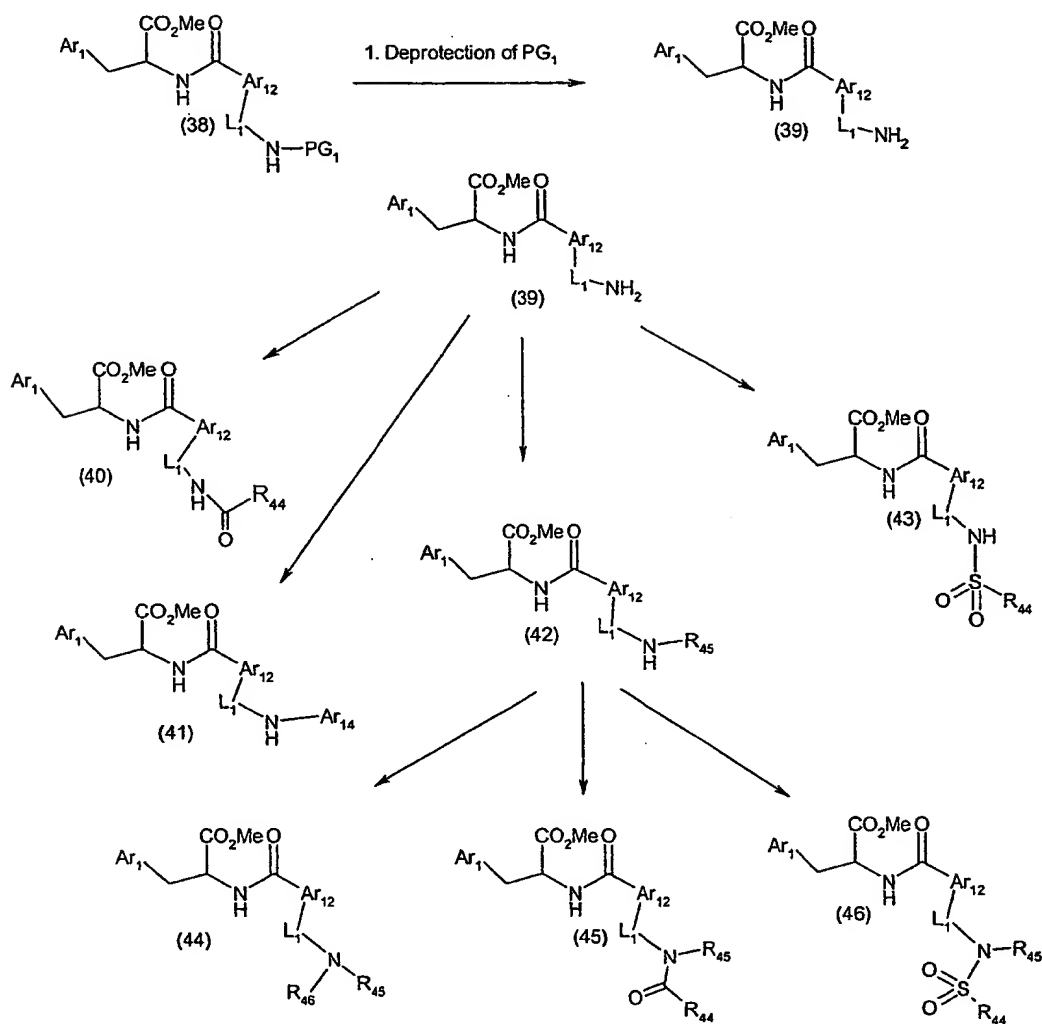


In Scheme XI, in another embodiment, is described the derivitization of aniline and amine nitrogen atoms.  $L_1$  is either a direct bond or a group such as an alkylene group. An amide derivative (38) may be prepared substantially in like manner as (30) and may be deprotected to afford (39). For example, where  $\text{PG}_1$  is a tert-butoxycarbonyl group, treatment of (38) with TFA followed by neutralization affords (39). (39) may be treated with  $\text{R}_{44}-\text{C}(\text{O})\text{OH}$  in the presence of a coupling agent such as HBTU or DCC to afford (40), or  $\text{R}_{44}-\text{COCl}$  in the presence of a weak base such as triethylamine, to afford (40). (39) may be treated with an aldehyde or ketone and a reducing agent such as sodium cyanoborohydride or sodium triacetoxyborohydride to afford (42). (39) may be treated with a sulfonyl chloride  $\text{R}_{44}\text{SO}_2\text{Cl}$  in the presence of a weak base such as triethylamine or pyridine to afford (43). (39) may also be treated with an activated aromatic halide such as 4-fluorobenzonitrile in the presence of a weak base such as DIEA, in a solvent such as DMF, at a temperature of from 25 °C to 120 °C, to afford the product of *ipso* halide displacement (41). Other activated or electron – deficient heteroaryl or aryl groups may be employed in this reaction. Alternately, where  $L_1$  is a direct bond, the aniline may be arylated by treatment of (39) with cuprous acetate and  $\text{Ar}_{14}-\text{B}(\text{OH})_2$ , and a weak base such as triethylamine, in a solvent such as DCM or 1,2-dichloroethane, to afford (41).

The derivative (42) may be reductively aminated a second time in the manner described above. (42) may also be acylated or sulfenylated as described above to afford (45) and (46), respectively.

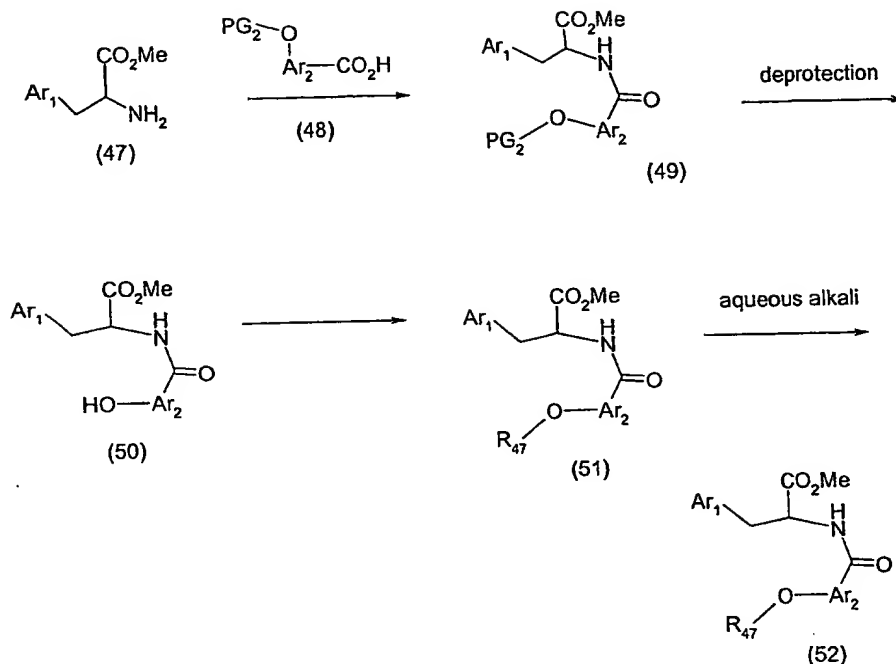
Scheme XI





- Scheme XII describes an additional embodiment. In Scheme XII, an amino ester and a protected phenolic aryl carboxylic acid or similar species are coupled as in Scheme 1.
- 5 The protecting group  $\text{PG}_2$  is removed, where  $\text{PG}_2$  is a hydroxyl or alcohol protecting group. For example, where  $\text{PG}_2$  is a tert-butyldimethylsilyl group, treatment of (49) with tetrabutylammonium fluoride in THF affords (50). (50) may be treated with a reagent such as but not limited to potassium carbonate and an alkyl halide  $\text{R}_{47}\text{-X}$ , where  $\text{R}_{47}$  is a group such as alkyl or substituted alkyl and X is a group such as bromo or iodo, to afford (51).
- 10 Alternately, where  $\text{R}_{47}$  is an activated or unactivated aromatic or heteroaromatic ring system and X is fluoro, treatment of (50) with  $\text{R}_{47}\text{-X}$  in the presence of a base such as but not limited to potassium carbonate in a solvent such as DMF, at a temperature of  $25^\circ\text{C}$  to  $120^\circ\text{C}$ , affords (51). Hydrolysis of the ester as described previously affords (52).

Scheme XII

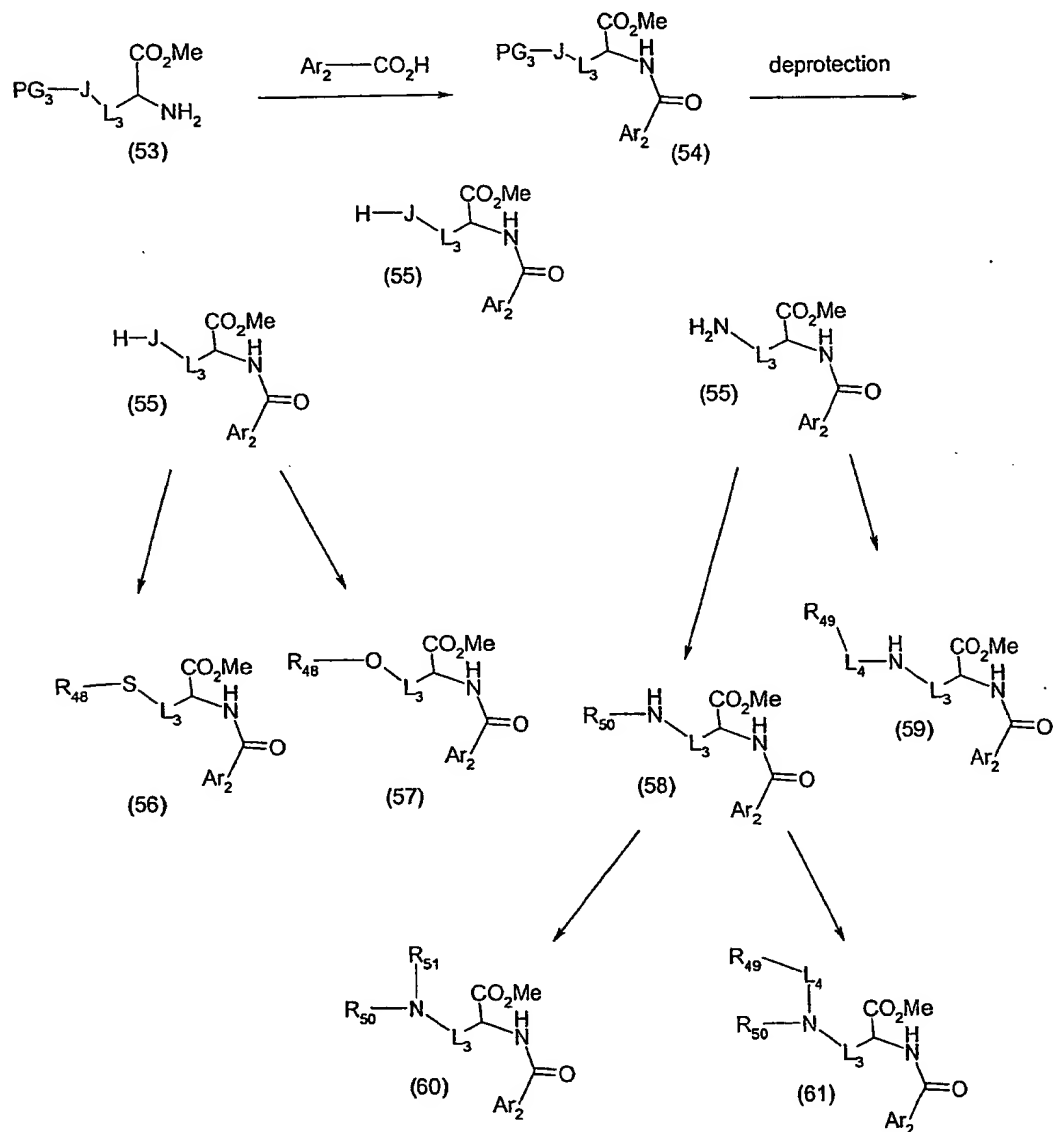


Scheme XIII describes another embodiment.  $\text{L}_3$  is a group such as  $-\text{alkylene}-$ . The amino ester (53) may be coupled with a carboxylic acid as described in Scheme I to afford 54. The protecting group  $\text{PG}_3$  may be removed. Where J is NH and  $\text{PG}_3$  is, for example, a tert-butoxycarbonylamino group, treatment of (54) with TFA or HCl in dioxane solvent affords the amine salt (55). Where J is O and  $\text{PG}_3$  is, for example, a benzyl group, treatment of (54) with a reagent such as but not limited to palladium on carbon in a solvent such as methanol or ethanol under a hydrogen atmosphere affords (55). Where J is S and  $\text{PG}_3$  is, for example, a trityl group, treatment of (54) with catalytic HCl or other acid in a solvent such as methanol under a nitrogen atmosphere affords (55). (55) where J is O or S may be alkylated with a reagent  $\text{R}_{48}\text{-X}$ , where  $\text{R}_{48}$  is (un)substituted alkyl and X is bromo or iodo or chloro, by reacting (55) with a base such as sodium hydride in a solvent such as THF or DMF and treating the reaction mixture with  $\text{R}_{48}\text{-X}$ . The resulting compounds (56) and (57) may be processed on to compounds of formula (I). Additionally, (56) may be oxidized to the sulfoxide or sulfone, respectively, by treatment with one or two equivalents of an oxidizing agent such as m-chloroperbenzoic acid in a solvent such as DCM or 1,2-dichloroethane. (55) may be treated with a carboxylic acid  $\text{R}_{49}\text{-COOH}$  and a coupling agent such as DCC under conditions described previously to afford (59), where  $\text{L}_4$  is  $-\text{C}(\text{O})-$ . Alternately, (55) may be treated with a sulfonyl chloride  $\text{R}_{49}\text{-SO}_2\text{Cl}$  in the presence of a base such as TEA or pyridine to afford (59), where  $\text{L}_4$  is  $-\text{SO}_2-$ . The amine (55) may be reductively aminated

employing a ketone or aldehyde under conditions described previously to afford (58), and (58) may be reductively aminated with a ketone or aldehyde to afford (60). Alternately, the amine (58) may be sulfonylated or acylated as described above to afford (61), where  $L_4$  is  $-SO_2-$  or  $-C(O)-$ .

5

Scheme XIII



The term "amino protecting group" as used herein refers to substituents of the amino group commonly employed to block or protect the amino functionality while reacting other functional groups on the compound. Examples of such amino-protecting groups include the

formyl group, the trityl group, the phthalimido group, the trichloroacetyl group, the chloroacetyl, bromoacetyl and iodoacetyl groups, urethane-type blocking groups such as benzyloxycarbonyl, 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-chlorobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 3-bromobenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-cyanobenzyloxy-carbonyl, 2-(4-xenyl)iso-propoxycarbonyl, 1,1-diphenyleth-1-yloxycarbonyl, 1,1-diphenylprop-1-yloxycarbonyl, 2-phenylprop-2-yloxycarbonyl, 2-(p-toluy)prop-2-yloxycarbonyl, cyclopentanyloxycarbonyl, 1-methylcyclopentanyloxycarbonyl, cyclohexanyloxycarbonyl, 1-methylcyclohexanyloxycarbonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-toluy)sulfonyl)ethoxycarbonyl, 2(methylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphino)ethoxycarbonyl, 9-fluorenylmethoxycarbonyl ("Fmoc"), t-butoxycarbonyl ("BOC"), 2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxalylmethoxycarbonyl, 4-acetoxybenzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-propoxycarbonyl, cyclopropylmethoxycarbonyl, 4-(decyloxy)benzyloxycarbonyl, isobomyloxycarbonyl, 1-piperidyloxycarbonyl and the like; the benzoylmethylsulfonyl group, the 2-(nitro)phenylsulfonyl group, the diphenylphosphine oxide group and like amino-protecting groups. The species of amino-protecting group employed is not critical so long as the derivatized amino group is stable to the condition of subsequent reaction(s) on other positions of the compound of Formula (I) and can be removed at the desired point without disrupting the remainder of the molecule. Preferred amino-protecting groups are the allyloxycarbonyl, the t-butoxycarbonyl, 9-fluorenylmethoxycarbonyl, and the trityl groups. Similar amino-protecting groups used in the cephalosporin, penicillin and peptide art are also embraced by the above terms. Further examples of groups referred to by the above terms are described by J. W. Barton, "Protective Groups In Organic Chemistry", J. G. W. McOmie, Ed., Plenum Press, New York, N.Y., 1973, and T. W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, N.Y., 1981. The related term "protected amino" or "protected amino group" defines an amino group substituted with an amino-protecting group discussed above.

The term "hydroxyl protecting group" as used herein refers to substituents of the alcohol group commonly employed to block or protect the alcohol functionality while reacting other functional groups on the compound. Examples of such alcohol -protecting groups include the 2-tetrahydropyranyl group, 2-ethoxyethyl group, the trityl group, the trichloroacetyl group, urethane-type blocking groups such as benzyloxycarbonyl, and the trialkylsilyl group, examples of such being trimethylsilyl, tert-butyl dimethylsilyl,

phenyldimethylsilyl, triisopropylsilyl and t-butyldimethylsilyl. The choice of alcohol-protecting group employed is not critical so long as the derivatized alcohol group is stable to the condition of subsequent reaction(s) on other positions of the compound of the formulae and can be removed at the desired point without disrupting the remainder of the molecule.

5 Further examples of groups referred to by the above terms are described by J. W. Barton, "Protective Groups In Organic Chemistry", J. G. W. McOmie, Ed., Plenum Press, New York, N.Y., 1973, and T. W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, N.Y., 1981. The related term "protected hydroxyl" or "protected alcohol" defines a hydroxyl group substituted with a hydroxyl - protecting group as discussed above.

10 The term "carboxyl protecting group" as used herein refers to substituents of the carboxyl group commonly employed to block or protect the -OH functionality while reacting other functional groups on the compound. Examples of such alcohol -protecting groups include the 2-tetrahydropyranyl group, 2-ethoxyethyl group, the trityl group, the allyl group, the trimethylsilylethoxymethyl group, the 2,2,2-trichloroethyl group, the benzyl group, and the  
15 trialkylsilyl group, examples of such being trimethylsilyl, t-butyldimethylsilyl, phenyldimethylsilyl, triisopropylsilyl and t-butyldimethylsilyl. The choice of carboxyl protecting group employed is not critical so long as the derivatized alcohol group is stable to the condition of subsequent reaction(s) on other positions of the compound of the formulae and can be removed at the desired point without disrupting the remainder of the molecule.  
20 Further examples of groups referred to by the above terms are described by J. W. Barton, "Protective Groups In Organic Chemistry", J. G. W. McOmie, Ed., Plenum Press, New York, N.Y., 1973, and T. W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, N.Y., 1981. The related term "protected carboxyl" defines a carboxyl group substituted with a carboxyl -protecting group as discussed above.

25

The general procedures used in the methods of the present invention are described below.

#### **General Experimental:**

30 LC-MS data was obtained using gradient elution on a Waters 600 controller equipped with a 2487 dual wavelength detector and a Leap Technologies HTS PAL Autosampler using an YMC Combiscreen ODS-A 50x4.6 mm column. A three minute gradient was run from 25% B (97.5% acetonitrile, 2.5% water, 0.05% TFA) and 75% A (97.5% water, 2.5% acetonitrile, 0.05% TFA) to 100% B. The mass spectrometer used was a Micromass ZMD

instrument. All data was obtained in the positive mode unless otherwise noted. <sup>1</sup>H NMR data was obtained on a Varian 400 MHz spectrometer.

Common names and definitions for resin reagents used in the disclosure are;

5

Merrifield	p-Chloromethyl polystyrene
Hydroxy-Merrifield	p-Hydroxymethyl polystyrene
Wang	(4-Hydroxymethyl)phenoxymethyl polystyrene
Wang carbonate	4-(p-nitrophenyl carbonate) phenoxymethyl polystyrene
10 Rink Resin	4-(2',4'-Dimethoxyphenyl-Fmco-aminomethyl)-phenoxy polystyrene resin
Wang Bromo Resin	(4-Bromomethyl)phenoxymethyl polystyrene
THP Resin	3,4-Dihydro-2H-pyran-2-ylmethoxymethyl polystyrene

15

Aldehyde resin can refer to the following:

	4-Benzyloxybenzaldehyde polystyrene
	3-Benzyloxybenzaldehyde polystyrene
20	4-(4-Formyl-3-methoxyphenoxy)butyryl-aminomethyl polystyrene
	2-(4-Formyl-3-methoxyphenoxy)ethyl polystyrene
	2-(3,5-dimethoxy-4-formylphenoxy)ethoxy-methyl polystyrene
	2-(3,5-dimethoxy-4-formylphenoxy)ethoxy polystyrene
	(3-Formylindolyl)acetamidomethyl polystyrene
25	(4-Formyl-3-methoxyphenoxy) grafted (polyethyleneglycol)-polystyrene; or
	(4-Formyl-3-methoxyphenoxy)methylpolystyrene.

Abbreviations used in the Examples are as follows:

30

APCI = atmospheric pressure chemical ionization  
 BOC = tert-butoxycarbonyl  
 BOP= (1-benzotriazolyl)tris(dimethylamino)phosphonium hexafluorophosphate  
 d = day

- DIAD = diisopropyl azodicarboxylate  
DCC = dicyclohexylcarbodiimide  
DCE = 1,2-dichloroethane  
DCM = dichloromethane  
5 DIC = diisopropylcarbodiimide  
DIEA = diisopropylethylamine  
DMA = N, N-dimethylacetamide  
DMAP = dimethylaminopyridine  
DME = 1,2 dimethoxyethane  
10 DMF = N, N-dimethylformamide  
DMPU = 1,3-dimethylpropylene urea  
DMSO = dimethylsulfoxide  
EDC = 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride  
EDTA = ethylenediamine tetraacetic acid  
15 ELISA = enzyme - linked immunosorbent assay  
ESI = electrospray ionization  
ether = diethyl ether  
EtOAc = ethyl acetate  
FBS = fetal bovine serum  
20 g = gram  
h = hour  
HBTU= O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate  
HMPA= hexamethylphosphoric triamide  
HOBt = 1-hydroxybenzotriazole  
25 Hz = hertz  
i.v. = intravenous  
kD = kiloDalton  
L = liter  
LAH = lithium aluminum hydride  
30 LDA = lithium diisopropylamide  
LPS = lipopolysaccharide  
M = molar  
 $m/z$  = mass to charge ratio  
mbar = millibar  
35 MeOH = methanol  
mg = milligram  
min = minute

	mL	= milliliter
	mM	= millimolar
	mmol	= millimole
	mol	= mole
5	mp	= melting point
	MS	= mass spectrometry
	N	= normal
	NMM	= N-methylmorpholine, 4-methylmorpholine
	NMR	= nuclear magnetic resonance spectroscopy
10	p.o.	= per oral
	PBS	= phosphate buffered saline solution
	PMA	= phorbol myristate acetate
	ppm	= parts per million
	psi	= pounds per square inch
15	R <sub>f</sub>	= relative TLC mobility
	rt	= room temperature
	s.c.	= subcutaneous
	SPA	= scintillation proximity assay
	TEA	= triethylamine
20	TFA	= trifluoroacetic acid
	THF	= tetrahydrofuran
	THP	= tetrahydropyranyl
	TLC	= thin layer chromatography
	TMSBr	= bromotrimethylsilane, trimethylsilylbromide
25	T <sub>r</sub>	= retention time

Thus, in an embodiment, the following compounds were synthesized according to the Schemes described herein.



## General procedure A:

To a solution of a carboxylic acid (1.0-1.5 mmol) in DMF (6 mL) was added an amino acid methyl ester (1.0-1.5 mmol), HBTU (1.0-1.5 mmol), and DIEA (2.0-3.0 mmol) and the mixture was stirred overnight. After completion of the reaction, sufficient amount of water was added and the mixture was extracted with ethyl acetate (3x15 ml). The combined organic layer was washed with water and brine, and then dried over sodium sulfate. The solvent was removed in vacuum to afford the amide, which was used for further transformation without further purification or purified by flash chromatography.

## General procedure B:

To a mixture of phenol and the aryl fluoride (2 eq) in DMF was added solid potassium carbonate (10 eq), and the mixture was heated at 80 °C for 12 h. After completion of the reaction, sufficient amount of water was added, and the mixture was extracted with ethyl acetate. The combined organic layer was washed with water and brine, dried over sodium sulfate. The solvent was removed in vacuum and the crude material obtained was purified by flash chromatography to afford the desired aryl ethers.

## General procedure C:

To a solution of ester in THF, CH<sub>3</sub>OH (4:1), 2N-lithium hydroxide solution (5 eq) was added, and the resulting reaction mixture was stirred at 0 °C for 30 minutes and then warmed to room temperature. After completion of the reaction, 2N HCl was used to neutralize the base, extracted with ethyl acetate, the organic layer was washed with brine, dried over sodium sulfate, and the solvent was removed in vacuum to afford the product.

## General procedure D:

To a solution of phenyl bromide in DME or Toluene were added corresponding boronic acid (5 eq), Pd (PPh<sub>3</sub>)<sub>4</sub> (0.5 % eq), 2N Na<sub>2</sub>CO<sub>3</sub> solution (5 eq). The mixture was heated at 75 °C for 12 h. After completion of the reaction, solvent was evaporated *in vacuo*. During the reaction, most of the ester was hydrolyzed to the corresponding acid. Therefore, crude product so obtained was re-esterified by dissolving it in CH<sub>3</sub>OH containing 1% of HCl. The mixture was refluxed for 6h and after the completion of the reaction, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (silica, CH<sub>2</sub>Cl<sub>2</sub>) to provide the desired ester. The resulting ester was hydrolyzed as described in procedure C yielding the acid.

## General procedure E:

To a solution of an aniline (1.0 mmol) in DCE (10 mL) was added an aldehyde (2.0-2.2 mmol), acetic acid (3.0 mmol) and sodium triacetoxyborohydride (2.5 mmol) or sodium cyanoborohydride and the mixture was stirred overnight. After completion of the reaction, 50 mL of DCM was added and the organic layer was washed with saturated sodium bicarbonate solution and brine, and then dried over sodium sulfate. The solvent was removed in vacuum to afford the amine, which was purified by flash chromatography.

General procedure F:

To a solution of an aniline (1.0 mmol) in DCM (10 mL) was added a sulfonyl chloride (1.0 mmol), and pyridine (10.0 mmol) and the mixture was stirred overnight. After completion of the reaction, 50 mL of DCM was added and the organic layer was washed with 1N HCl, saturated sodium bicarbonate solution and brine, and then dried over sodium sulfate. The solvent was removed in vacuum to afford the sulfonamide, which was purified by flash chromatography.

General procedure G:

A flask is charged with phenol or aniline (1.0 equiv),  $\text{Cu}(\text{OAc})_2$  (1.0 equiv), arylboronic acid (1.0-3.0), and powdered 4 Å molecular sieves. The reaction mixture is diluted with  $\text{CH}_2\text{Cl}_2$  to yield a solution approximately 0.1M in phenol or aniline, and the  $\text{Et}_3\text{N}$  (5.0 equiv) is added. After stirring the colored heterogeneous reaction mixture for 24 h at 25 °C under ambient atmosphere, the resulting slurry is filtered and the diaryl ether or diaryl amine is isolated from the organic filtrate by flash chromatography.

General procedure H:

To a solution of a phenol (1.0 mmol) in DMF (5 mL) was added an alkyl halide (1.2 mmol) (a catalytic amount of NaI is added for alkyl chlorides), and potassium carbonate (2.5 mmol) and the mixture heated at 70 °C overnight. After completion of the reaction, 5 mL of ethyl acetate and 5 mL of water was added. The organic layer was washed with water, and then dried over sodium sulfate. The solvent was removed in vacuum to afford the ether, which was purified by flash chromatography.

General Procedure I:

To a solution of ester in THF was added lithium hydroxide (3-4eq), water, and methanol. The ratio of THF/water/methanol is 4:1:1. The reaction mixture was stirred at RT for 1-1.5 h. A 10% solution of citric acid was added to adjust the pH between 6-7. Ethyl acetate was added and the organic layer is separated. The aqueous layer was extracted

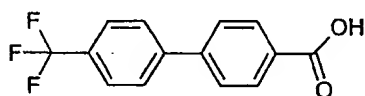
with ethyl acetate twice. The combined organic layer was washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated under reduced pressure to give the product.

General Procedure J:

5 To a stirring solution of an aniline (2 mmol) dissolved in DCM containing pyridine (4 mmol), was added acid chloride (2.5 mmol) at 0 °C. The reaction mixture was stirred at rt for 3 h, extracted with DCM, washed with 1M HCl and brine evaporation followed by column chromatography purification gave amide.

10 The above general methods are for illustration only; Alternative conditions that may optionally be used include: Use of alternative solvents, alternative stoichiometries of reagents, alternative reaction temperatures and alternative methods of purification.

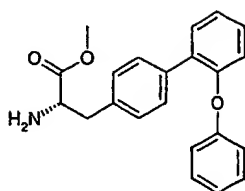
15 Synthesis of 4'-Trifluoromethyl-biphenyl-4-carboxylic acid



20 The title compound was made as described in general procedure D using 4-bromo benzoic acid (10g, 49.4 mmol), 4-trifluoromethyl phenylboronic acid (14.17g, 74.61 mmol), palladium tetrakis-triphenylphosphine (5.7g, 4.974 mmol) and 2N  $\text{Na}_2\text{CO}_3$  aq. solution (150 mL, 149.2 mmol) in 500 ml of Toluene. After the reaction is complete, the reaction mixture was neutralized with 2N HCl then filtered. The resulting solid was dissolved in ethyl acetate then passed through a short column of silica gel giving 9.7 g (75%) of the compound as a  
25 white solid.

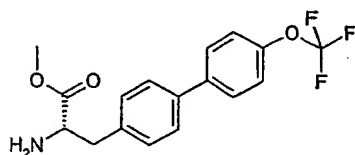
Synthesis of Amino Acids:

30 (2S)-Amino-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester



5 The title compound was prepared following the procedure D using (L)-4-bromophenylalanine (8.55g, 35.0 mmol), 2-phenoxyphenyl boronic acid (10.00g, 46.73 mmol), and palladium tetrakis-triphenylphosphine (4.0 g, 10% mmol) ) and 2N Na<sub>2</sub>CO<sub>3</sub> aq. solution (70 mL, 140 mmol) in 140 ml of DME. After removal of solvents, the solid was washed with ether to afford the title compound as the HCl salt (10.0 g, 26.20 mmol, 75% yield).

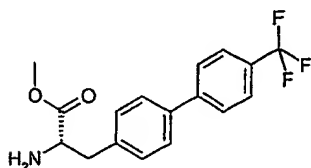
10 (2S)-Amino-3-(4'-trifluoromethoxy-biphenyl-4-yl)-propionic acid methyl ester



15 The title compound was prepared following the procedure D using (L)-4-bromophenylalanine (8.0 g, 32.7 mmol), 4-trifluoromethoxybenzene boronic acid (10.1 g, 49.1 mmol), palladium tetrakis-triphenylphosphine (3.7 g, 3.2 mmol), and Na<sub>2</sub>CO<sub>3</sub> (2.0 N, 80.0 mL, 160 mmol) in DME (300 mL). After removal of solvent, the solid was washed with ether to afford the title compound as the HCl salt (10.8 g, 28.7 mmol, 88% yield).

20

(2S)-Amino-3-(4'-trifluorobiphenyl-4-yl)-propionic acid methyl ester



25

The title compound was prepared exactly following the procedure D using (L)-4-bromophenylalanine (9.0 g, 36.8 mmol), 4-trifluoromethylbenzene boronic acid (10.48 g, 55.2 mmol), palladium tetrakis-triphenylphosphine (4.25 g, 3.6 mmol), and aqueous Na<sub>2</sub>CO<sub>3</sub> (2.0 N, 90.0 mL, 185 mmol) in DME (300 mL). After removal of solvent, the solid was washed with ether to afford the title compound as the HCl salt (10.5 g, 29.2 mmol, 79% yield).

#### Example 1

##### 3-Biphenyl-4-yl-(2S)-[(isoquinoline-3-carbonyl)-amino]-propionic acid

2-L-amino-3-biphenyl-4-yl-propionic acid methyl ester (100 mg, 0.1 mmol) was reacted with isoquinoline-3-carboxylic acid (78 mg, 0.5 mmol) as described in general procedure A. The resulting compound was hydrolyzed according to general procedure C to afford the title product (132 mg, 81%) as a white solid.

<sup>1</sup>H-NMR (400 MHz, CD<sub>3</sub>COCD<sub>3</sub>): 3.38(dd, 1H), 3.47 (dd, 1H), 5.09 (m, 1H), 7.32 (m, 1H), 7.42 (m, 4H), 7.60 (m, 4H), 7.82 (m, 1H), 7.89 (m, 1H), 8.17 (m, 1H), 8.23 (m, 1H), 8.58 (s, 1H), 8.76 (m, 1H), 9.30 (d, 1H); LC/MS (*m/z*): 397(M+1)<sup>+</sup>.

#### Example 2

(2S)-[(Isoquinoline-3-carbonyl)-amino]-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid 3-(4-Bromo-phenyl)-(2S)-[(isoquinoline-3-carbonyl)- amino]-propionic acid methyl ester (720 mg, 90%) was prepared starting from 2-L-amino-3-(4-bromo-phenyl)-propionic acid methyl ester (500 mg, 1.9 mmol) and isoquinoline -3-carboxylic acid (400 mg, 2.3 mmol) according to general procedure A.

The resulting amide (100 mg, 0.24 mmol) was reacted with 4-trifluoromethylphenyl boronic acid (95 mg, 0.5 mmol) as described in general procedure D yielding the title compound (80 mg, 80%) as a white solid.

<sup>1</sup>H-NMR(400 MHz, CDCl<sub>3</sub>): 3.33(m, 2H), 5.08 (m, 1H), 7.11 (d, 1H ), 7.36 (t, 2H), 7.49 (m, 1H), 7.61 (s, 2H), 7.77 (m, 3H), 8.00 (m, 3H), 8.60 (d, 1H), 8.75 (m, 1H), 9.16 (s, 1H); LC/MS (*m/z*): 465(M+1)<sup>+</sup>.

#### Example 3

(2S)-[(Isoquinoline-3-carbonyl)-amino]-3-(3,5'-bistrifluoromethyl-biphenyl-4-yl)-propionic acid 3-(4-Bromo-phenyl)-(2S)-[(isoquinoline-3-carbonyl)-amino]-propionic acid methyl ester (100 mg, 0.24 mmol) prepared as in example 2 was reacted with 3,5-

bis(trifluoromethyl)phenyl boronic acid (129 mg, 0.5 mmol) as described in general procedure D to afford the title compound (100 mg, 79%) as a white solid.

<sup>1</sup>H-NMR(400 MHz, CDCl<sub>3</sub>): 3.36(dd, 1H), 3.48 (dd, 1H), 5.18 (m, 1H), 7.40 (d, 2H), 7.51 (d, 2H), 7.74 (m, 2H), 7.79 (m, 1H), 7.94 (m, 2H), 8.00 (m, 2H), 8.59 (s, 1H), 8.74 (d, 1H), 9.14 (s, 1H); LC/MS (*m/z*): 533(M<sup>+</sup>+1)<sup>+</sup>.

#### Example 4

(2S)-[(Isoquinoline-3-carbonyl)-amino]-3-(4'-methoxy-biphenyl-4-yl)-propionic acid

3-(4-Bromo-phenyl)-(2S)-[(isoquinoline-3-carbonyl)-amino]-propionic acid methyl ester (100 mg, 0.24 mmol) prepared as in example 2 was reacted with 4-methoxyphenyl boronic acid (76 mg, 0.5 mmol) as described in general procedure D yielding the title compound (84 mg, 82%) as a white solid.

<sup>1</sup>H-NMR(400 MHz, CDCl<sub>3</sub>): 3.32(m, 2H), 3.81 (s, 3H), 5.12 (m, 1H), 6.91 (m, 1H), 7.11 (d, 1H), 7.26 (m, 2H), 7.32 (m, 2H), 7.46 (m, 2H), 7.74 (m, 3H), 7.98 (m, 2H), 8.59 (d, 1H), 8.74 (m, 1H), 9.14 (s, 1H); LC/MS (*m/z*): 427(M+1)<sup>+</sup>.

#### Example 5

3-[4-(4'-Cyano-phenoxy)-phenyl]-(2S)-[(isoquinoline-3-carbonyl)-amino]-propionic acid

3-(4-Hydroxyphenyl)-(2S)-[(isoquinoline-3-carbonyl)-amino]-propionic acid methyl ester (807 mg, 90%) was prepared from (2S)-amino-3-(4-hydroxy-phenyl)-propionic acid methyl ester (500 mg, 3.0 mmol) and isoquinoline-3-carboxylic acid (530 mg, 2.3 mmol) according to general procedure A.

The resulting amide (100 mg, 0.28 mmol) was reacted with 4-cyano fluorobenzene (36 mg, 0.30 mmol) as described in general procedure B. The resulting aryl ether was hydrolyzed as described in general procedure C yielding the title compound (47 mg, 72%) as a white solid.

<sup>1</sup>H-NMR(400 MHz, CDCl<sub>3</sub>): 3.30(dd, 1H), 3.44 (dd, 1H), 5.10 (m, 1H), 6.96 (m, 3H), 7.27 (m, 1H), 7.31 (d, 2H), 7.53 (d, 2H), 7.77 (m, 2H), 7.99 (d, 1H), 8.05 (d, 1H), 8.59 (s, 1H), 8.70 (d, 1H), 9.15 (s, 1H); LC/MS (*m/z*): 438(M+1)<sup>+</sup>.

#### Example 6

3-[4-(4'-Nitro-phenoxy)-phenyl]-(2S)-[(isoquinoline-3-carbonyl)-amino]-propionic acid

3-(4-Hydroxy-phenyl)-(2S)-[(isoquinoline-3-carbonyl)-amino]-propionic acid methyl ester (50 mg, 0.15 mmol) prepared as in example 5 was reacted with 4-nitro-fluorobenzene (42 mg, 0.30 mmol) as described in general procedure B and hydrolyzed as described in general procedure C yielding the title compound (49 mg, 71%) as a light yellow solid. LC/MS (*m/z*): 456 (M+1)<sup>+</sup>

By analogous methods to those described above the following Examples were synthesized.

EXAMPLE	NAME	LC/MS( <i>m/z</i> )
7	3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-(2S)-[(isoquinoline-3-carbonyl)-amino]-propionic acid	449
8	3-(4'-Cyano-biphenyl-4-yl)-(2S)-[(isoquinoline-3-carbonyl)-amino]-propionic acid	422
9	(2S)-[(Isoquinoline-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionic acid	465
10	(2S)-[(Isoquinoline-3-carbonyl)-amino]-3-(3'-nitro-biphenyl-4-yl)-propionic acid	442

#### 10 Example 11

3-Biphenyl-4-yl-(2S)-[(7-bromo-isoquinoline-3-carbonyl)-amino]-propionic acid

To a solution of 4-bromophthalic acid (3.0 g, 12.24 mmol) in 30 mL of THF was added a solution of borane-THF complex (1.0M) dropwise at 0 °C. The solution was warmed to rt and stirred for 3 h. The reaction mixture was quenched by addition of HCl (2N) at 0 °C. The product was extracted with ethyl acetate and washed with sat. NaCl, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure to afford 2.8 g (100%) of 4-bromo-2-hydroxymethylbenzyl alcohol as a colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 7.28 (m, 2 H), 7.26 (m, 1 H), 4.69 (s, 4 H), 2.80 (bs, 2 H).

To a solution of oxalyl chloride (2.37 mL, 4.607 mmol) in DCM (20 mL) was added dropwise DMSO (1.95 mL) at -78 °C. The mixture was stirred at -78 °C for 30 min and a solution of the diol (1.00 g, 4.607 mmol) was added dropwise. The reaction mixture was stirred for 2 hr and TEA (11.5 mL) was added. The reaction mixture was warmed to rt and water was added. The organic layer was separated and washed with sat. NaCl, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure to give 4-bromo-benzene-1,2-dicarbaldehyde as a yellow oil (0.450 g, 46%).

A mixture of 4-bromo-benzene-1,2-dicarbaldehyde (0.450 g, 2.137 mmol), diethylamino malonate (0.452 g, 2.137 mmol), and sodium ethoxide (0.218 g, 3.20 mmol) in

anhydrous ethanol (15 mL) was refluxed for 4 hr. The solution was cooled to rt and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, 0.5% MeOH in  $\text{CHCl}_3$ ) to obtain 0.460 g (78%) of the 7-bromo-isoquinoline-3-carboxylic acid ethyl ester which was hydrolyzed according to general procedure C yielding the 0.350 g (85%) of 7-bromo-isoquinoline-3-carboxylic acid as a white solid. LC/MS ( $m/z$ ): 253 ( $M+1$ )<sup>+</sup>.

(2S)-amino-3-biphenyl-4-yl-propionic acid methyl ester (340 mg, 13.9 mmol) was reacted with 7-bromo-isoquinoline-3-carboxylic acid (350 mg, 13.9 mmol) as described in general procedure A. The resulting compound was hydrolyzed by following general procedure C yielding the title compound (132 mg, 81%) as a white solid.

#### Example 12

3-Biphenyl-4-yl-(2S)-[7-(4-trifluoromethyl-phenyl)-isoquinoline-3-carbonyl]-amino)-propionic acid

#### Example 11

(50 mg, 0.1 mmol) was reacted with 4-trifluoromethylphenyl boronic acid (42.5 mg, 0.3 mmol) as described in general procedure D yielding the title compound (45 mg, 80%) as a white solid.

<sup>1</sup>H-NMR (400 MHz,  $\text{CDCl}_3$ ): 8.94 (s, 1 H), 8.75 (3s, 1 H), 8.67 (m, 1 H), 8.47 (m, 1 H), 7.82 (m, 2 H), 7.51 (m, 12 H), 5.07 (m, 1 H), 3.28 (m, 2 H); LC/MS ( $m/z$ ): 541 ( $M+1$ )<sup>+</sup>.

#### Example 13

3-Biphenyl-4-yl-(2S)-[7-(3-chloro-4-fluoro-phenyl)-isoquinoline-3-carbonyl]-amino)-propionic acid

#### Example 11

(50 mg, 0.1 mmol) was reacted with 3-chloro-4-fluoro-phenyl boronic acid (109 mg, 0.3 mmol) as described in general procedure D yielding the title compound (45 mg, 80%) as a white solid.

<sup>1</sup>H-NMR (400 MHz,  $\text{CDCl}_3$ ): 9.11 (s, 1 H), 8.74 (s, 1 H), 8.58 (m, 1 H), 8.01 (m, 1 H), 7.82-7.26 (m, 13 H), 5.13 (m, 1 H), 3.44 (m, 2 H); LC/MS ( $m/z$ ): 541 ( $M+1$ )<sup>+</sup>.

#### Example 14



## 2-Biphenyl-4-yl-N-(1-bromo-isoquinolin-3-yl)-acetamide

To a solution of 4-biphenylacetic acid (1.0g, 4.7 mmol) in 10 ml of anhydrous DMF was added HBTU (2.1g, 5.7 mmol) and 1.0 ml of DIEA. The mixture was stirred at room temperature for 10 min, and then 1-bromo-3-isoquinolinamine (0.68g, 4.7 mmol) was added. After stirring over night, the mixture was poured into water, acidified with 10% citric acid, and extracted with ethyl acetate. The organic extracts were washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>. After the condensation of the solvent, the residue was purified by flash column chromatography (SiO<sub>2</sub>, 1:1 hexane:ethyl acetate) to provide the title compound (1.7g, 86%) as a light yellow solid.

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): 3.83 (s, 3H), 7.33-7.37 (m, 1H), 7.42-7.48 (m, 4H), 7.52-7.58 (m, 1H), 7.60-7.64 (m, 4H), 7.65-7.70 (m, 1H), 7.80 (d, 1H), 7.61 (s, 1H), 8.18 (d, 1H), 8.56 (s, 1H); LC/MS (*m/z*): 418 (M+1)<sup>+</sup>.

## Example 15

## 2-Biphenyl-4-yl-N-[1(4-trifluoromethyl-phenyl)-isoquinolin-3-yl]-acetamide

A mixture of Example 14 (0.1g, 0.24 mmol), 3-trifluoromethylphenylboronic acid (0.14 g, 0.72 mmol), Pd (PPh<sub>3</sub>)<sub>4</sub> (0.028g, 0.024 mmol) and 2N Na<sub>2</sub>CO<sub>3</sub> solution (0.1 ml) in DME was heated at 75 °C for 12 h under nitrogen. The reaction mixture was cooled, and the solvent was evaporated. The resulting residue was purified by flash column chromatography (SiO<sub>2</sub>, 10% ethyl acetate in hexane) to provide the title compound (0.1g, 87%) as a light yellow solid.

<sup>1</sup>H-NMR(400 MHz, CDCl<sub>3</sub>): 3.85(s, 3H), 7.34-7.39 (m, 1H), 7.42-7.46 (m, 5H), 7.56-7.67 (m, 6H), 7.77 (d, 1H), 7.8 (d, 1H), 7.85-7.91 (m, 3H), 8.15 (s, 1H), 8.65 (s, 1H); LC/MS (*m/z*): 483 (M+1)<sup>+</sup>.

## Example 16

## N-[1(4-aminomethyl-phenyl)-isoquinolin-3-yl]-2-biphenyl-4-yl-acetamide

The title compound was prepared (0.1 g, 85%) from Example 14 (0.1 g, 0.24 mmol) employing 4-amino methyl phenylboronic acid (0.1 g, 0.72 mmol) as described in Example 15. LC/MS (*m/z*): 444 (M+1)<sup>+</sup>.

## Example 17

3-Biphenyl-4-yl-(2S)-[4-(2-biphenyl-4-yl-ethylamino)-quinazoline-2-carbonyl]-amino-propionic acid

2.18 g (10 mmol) of 2-ethoxycarbonylquinazolin-4-one was suspended in 20 ml of phosphorus oxychloride. The mixture was refluxed for one hour, and the solvent was removed by rotary evaporation. The resulting residue was dissolved in ethyl acetate, and the obtained solution was washed with saturated sodium bicarbonate solution three times, dried over anhydrous sodium sulfate, filtered, and evaporated to give 2.13 g (90% mmol) of 2-ethoxycarbonyl-4-chloroquinazoline as a pale-yellow solid. LC/MS (*m/z*) 237 (*M*+1)<sup>+</sup>.

236 mg (1.0 mmol) of 2-ethoxycarbonyl-4-chloroquinazoline obtained above, 210 mg (1.05 mmol) of biphenylethylamine and 1.0 ml (5.74 mmol) of diisopropylethylamine were mixed with 10 ml of isopropyl alcohol. The mixture was refluxed for 12 hours. The residue obtained after removing the solvent was purified by chromatography (5% ethyl acetate in DCM) to give 360 mg (0.9 mmol) of 2-ethoxycarbonyl-4-biphenylethylaminoquinazoline as a white solid. The ethyl ester was hydrolyzed according to general procedure C yielding the 295 mg (90%) of 4-biphenylethylaminoquinazoline-2-carboxylic acid as a white solid. LC/MS (*m/z*): 398 (*M*+1)<sup>+</sup>.

To 200 mg (~0.2 mmol) of Wang resin (1.1 mmol/g) loaded with L-4-biphenylalanine were added 220 mg of (0.6 mmol) 4-biphenylethylaminoquinazoline-2-carboxylic acid, 0.6 mL (0.6 mmol) of 1.0 *M* DIC in DMF, 0.6 mL (0.6 mmol) of 1.0 *M* HOBt in DMF, and a catalytic amount of DMAP. The resulting mixture was left on shaker overnight. The resin was washed with DMF, MeOH, DCM three times of each and cleaved with 20% TFA in DCM. The residue obtained after removing the solvent was purified by chromatography (10% methanol in DCM) to give 72 mg (60%) of the title compound.

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): 2.91 (t, 2H), 3.30-3.36 (m, 2H), 3.90-4.00 (m, 2H), 4.98 (t, 1H), 7.06 (d, 2H), 7.12-7.21 (m, 4H), 7.22-7.31 (m, 9H), 7.33-7.38 (m, 3H), 7.72 (td, 1H), 7.90-7.96 (m, 2H), 8.22 (d, 1H); LC/MS (*m/z*): 593 (*M*+1)<sup>+</sup>.

#### Example 18

3-Biphenyl-4-yl-(2S)-{[4-*tert*-butyl-benzylamino]-quinazoline-2-carbonyl]-amino}- propionic acid

4-*tert*-butyl benzyl aminoquinazoline-2-carboxylic acid (290 mg, 90%) was synthesized from 236 mg (1.0 mmol) of 2-ethoxycarbonyl-4-chloroquinazoline, 210 mg (1.05 mmol) of 4-*tert*-butyl benzylamine and 1.0 ml (5.74 mmol) of diisopropylethylamine as described in Example 17.

4-*tert*-butyl benzyl aminoquinazoline-2-carboxylic acid (290 mg, 0.6 mmol) so obtained was reacted with 200 mg (~0.2 mmol) of Wang resin (1.1 mmol/g) loaded with L-4-biphenylalanine as described in Example 17 yielding the title compound (70mg, 60%). LC/MS (*m/z*) 559 (*M*+1)<sup>+</sup>.

## Example 19

3-Biphenyl-4-yl-(2S)-[[6-(3-chloro-4-fluoro-phenyl)-pyridine-2-carbonyl]-amino]-propionic acid

5           3-Biphenyl-4-yl-(2S)-[[6-bromo-pyridine-2-carbonyl]-amino]-propionic acid methyl ester (1.5g, 90%) was prepared by following general procedure A from commercially available 5-bromo picolinic acid (0.95g, 4.7 mmol) and (2S)-amino-3-biphenyl-4-yl-propionic acid methyl ester (1.0g, 3.9 mmol).

10           The above compound (80 mg, 0.20 mmol) was reacted with 3-chloro-4-fluoro phenylboronic acid ( 87 mg, 0.5 mmol) as described in general procedure D yielding 3-Biphenyl-4-yl-2-[[6-(3-chloro-4-fluoro-phenyl)-pyridine-2-carbonyl]-amino]-propionic acid (75 mg, 79%) as a light yellow solid. LC/MS (*m/z*): 475 (*M*+1)<sup>+</sup>.

## Example 20

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3-Biphenyl-4-yl-(2S)-[[6-(3-chloro-4-fluorophenyl)-pyridine-2-carbonyl]-amino]-propionic acid

20           3-Biphenyl-4-yl-(2S)-[[6-bromo-pyridine-2-carbonyl]-amino]-propionic acid methyl ester (80 mg, 0.20 mmol) was reacted with 4-trifluoro methyl phenylboronic acid (87 mg, 0.5 mmol) as described in general procedure D to afford the title compound (75 mg, 79%) as a light yellow solid. LC/MS (*m/z*): 475 (*M*+1)<sup>+</sup>.

By analogous methods to those described above the following compounds were synthesized.

EXAMPLE	NAME	LC/MS( <i>m/z</i> )
21	3-Biphenyl-4-yl-(2S)-[[6-(4-trifluoromethoxy-phenyl)-pyridine-2-carbonyl]-amino]-propionic acid	507
22	3-Biphenyl-4-yl-(2S)-[[6-(4-fluoro-3-methyl-phenyl)-pyridine-2-carbonyl]-amino]-propionic acid	455
23	(2S)-[[6-(4-Amino-phenyl)-pyridine-2-carbonyl]-amino]-3-biphenyl-4-yl-propionic acid	438
24	3-Biphenyl-4-yl-(2S)-[[6-(3-cyano-phenyl)-pyridine-2-carbonyl]-amino]-propionic acid	448
25	3-Biphenyl-4-yl-(2S)-[[6-(4-methanesulfonyl-	501

EXAMPLE	NAME	LC/MS(m/z)
	phenyl)-pyridine-2-carbonyl]-amino}-propionic acid	
26	3-Biphenyl-4-yl-(2S)-[[6-(4-methoxy-phenyl)-pyridine-2-carbonyl]-amino}-propionic acid	453
27	3-Biphenyl-4-yl-(2S)-[[6-(3-carbamimidoyl-phenyl)-pyridine-2-carbonyl]-amino}-propionic acid	465
28	3-Biphenyl-4-yl-(2S)-[[6-(4-phenoxy-phenyl)-pyridine-2-carbonyl]-amino}-propionic acid	515
29	3-Biphenyl-4-yl-(2S)-[[6-(4-tert-butyl-phenyl)-pyridine-2-carbonyl]-amino}-propionic acid	479

## Example 30

3-Biphenyl-4-yl-(2S)-[[5-(3-chloro-4-fluoro-phenyl)-pyridine-2-carbonyl]-amino}-propionic acid

5        3-Biphenyl-4-yl-(2S)-[[5-bromo-pyridine-2-carbonyl]-amino}-propionic acid methyl ester (1.5g, 90%) was prepared by following general procedure A from commercially available 5-bromo picolinic acid (0.9g, 4.7 mmol) and (2S)-amino-3-biphenyl-4-yl-propionic acid methyl ester (1.0g, 3.9 mmol).

10        The above compound (80 mg, 0.20 mmol) was reacted with 3-chloro-4-fluoro phenylboronic acid ( 87 mg, 0.5 mmol) as described in general procedure D yielding the title compound ( 75 mg, 79%) as a light yellow solid. LC/MS (m/z): 475(M+1)<sup>+</sup>.

By analogous methods to those described above the following compounds were synthesized.

EXAMPLE	NAME	LC/MS(m/z)
31	3-Biphenyl-4-yl-(2S)-[[5-(4-trifluoromethyl-phenyl)-pyridine-2-carbonyl]-amino}-propionic acid	491
32	3-Biphenyl-4-yl-(2S)-[[5-(4-methoxy-phenyl)-pyridine-2-carbonyl]-amino}-propionic acid	453

## Example 33

3-Biphenyl-4-yl-(2S)-[[4-(3-chloro-4-fluoro-phenyl)-pyridine-2-carbonyl]-amino}-propionic acid

3-Biphenyl-4-yl-(2S)-[(4-chloro-pyridine-2-carbonyl)-amino]-propionic acid methyl ester (1.26g, 85%) was prepared by following general procedure A from commercially available 4-chloro picolinic acid (0.7g, 4.4 mmol) and (2S)-amino-3-biphenyl-4-yl-propionic acid methyl ester (1.0g, 3.9 mmol).

- 5        The above compound (80 mg, 0.20 mmol) was reacted with 3-chloro 4-fluoro phenylboronic acid (70 mg, 0.40 mmol) as described in general procedure D yielding the title compound (48 mg, 51%) as a white solid. LC/MS (*m/z*): 475 (M+1)<sup>+</sup>.

#### Example 34

10

3-Biphenyl-4-yl-(2S)-[(4-(4-methoxy-phenyl)-pyridine-2-carbonyl]-amino]-propionic acid methyl ester (80 mg, 0.20 mmol) was reacted with 4-methoxy phenylboronic acid (61 mg, 0.40 mmol) as described in general procedure D to afford the title compound (42 mg, 46%) as a light yellow solid. LC/MS (*m/z*): 453 (M+1)<sup>+</sup>.

15

By analogous methods to those described above the following compounds were synthesized

EXAMPLE	NAME	LC/MS( <i>m/z</i> )
35	3-Biphenyl-4-yl-(2S)-[(4-(4-trifluoromethyl-phenyl)-pyridine-2-carbonyl]-amino]-propionic acid	491
36	3-Biphenyl-4-yl-(2S)-[(4-(3-trifluoromethyl-phenyl)-pyridine-2-carbonyl]-amino]-propionic acid	491

#### Example 37

20

3-Hydroxy-naphthalene-2-carboxylic acid (2-biphenyl-4yl-ethyl)-amide

To 40.40 g (200 mmol) of Methyl 3-hydroxy-2-naphthoate, 11.0 g (220 mmol) of sodium methoxide in 500 mL of anhydrous DMA was added 13.30 g (71 mmol) of Merrifield resin. The mixture was heated at 110 °C overnight. The resin was washed with H<sub>2</sub>O, DMF, MeOH, DCM three times each, and dried. The resulting resin-bound methyl naphthoate was hydrolyzed with LiOH/H<sub>2</sub>O/THF/ethanol at rt for 3 days.

25

To 1.0 g (2.5 mmol) of above resulting resin-bound naphthoic acid was added mixture of 1.5 g (7.5 mmol) of 4-bromophenethylamine, 7.5 mL (7.5 mmol) of 1.0 M DIC in DMF, 7.5 mL (7.5 mmol) of 1.0 M HOBt in DMF, and a catalytic amount of DMAP. The resulting mixture was left on a shaker overnight. The resin was washed with DMF, MeOH,

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DCM three times of each to give the resin-bound *N*-2-(4-bromophenyl)ethyl-3-hydroxyl-2-naphthamide.

To 0.05 g (0.1 mmol) of above resin-bound *N*-2-(4-Bromophenyl)ethyl-3-hydroxyl-2-naphthamide in 2.0 mL of DME were added 36.6 mg (0.3 mmol) of phenylboronic acid, 30 mg (0.03 mmol) of Pd(PPh<sub>3</sub>)<sub>4</sub>, and 0.3 mL (0.6 mmol) of 2*N* Na<sub>2</sub>CO<sub>3</sub> solution. The mixture was heated to 80 °C for 12 h. The resin was washed with H<sub>2</sub>O, DMF, MeOH, DCM three times of each and cleaved with TMSBr/TFA/DCM (1:1:5) at rt for 4h. The residue obtained after removing the solvent was purified by chromatography (100% methylene chloride) to give 22 mg (60%) of the title compound.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 3.04 (t, 2H), 3.82 (dd, 2H), 6.60 (m, 1H), 7.28-7.38 (m, 5H), 7.43-7.49 (m, 3H), 7.59-7.61 (m, 4H), 7.67-7.70 (m, 2H), 7.81 (s, 1H), 11.75 (s, 1H); LC/MS (*m/z*): 368 (M+1)<sup>+</sup>.

#### Example 38

3-[(3'-Chloro-4'-fluoro)-biphenyl-4-yl]-(2*S*)-[(3-hydroxy-naphthalene-2-carbonyl)-amino]-propionic acid

To 1.0 g (2.5 mmol) of resin-bound naphthoic acid obtained in Example 37 was added 1.95 g (7.5 mmol) of L-4-bromophenylalanine methyl ester, 7.5 mL (7.5 mmol) of 1.0 *M* DIC in DMF, 7.5 mL (7.5 mmol) of 1.0 *M* HOBT in DMF, and a catalytic amount of DMAP. The resulting mixture was left on a shaker overnight. The resin was washed with DMF, MeOH, DCM three times of each to give resin-bound 3-(4-bromophenyl) ethyl-2-[3-(hydroxy-naphthalene-2-carbonyl)amino]-propionic acid methyl ester.

To 0.05 g (0.1 mmol) of the above resin-bound 3-(4-bromophenyl)ethyl-(2*S*)-[3-(hydroxy-naphthalene-2-carbonyl)-amino]-propionic acid methyl ester in 2.0 mL of DME were added 52.0 mg (0.3 mmol) of 3-chloro-4-fluorophenylboronic acid, 30 mg (0.03 mmol) of Pd(PPh<sub>3</sub>)<sub>4</sub>, and 0.3 mL (0.6 mmol) of 2*N* Na<sub>2</sub>CO<sub>3</sub> solution. The mixture was heated to 80 °C for 12 h. The resin was washed with H<sub>2</sub>O, DMF, MeOH, DCM three times of each and cleaved with TMSBr/TFA/DCM (1:1:5) at rt for 4h. The residue obtained after removing the solvent was purified by chromatography (DCM) to give 30 mg (60%) of 3-[(3'-Chloro-4'-fluoro)-biphenyl-4-yl]-(2*S*)-[(3-hydroxy-naphthalene-2-carbonyl)-amino]-propionic acid methyl ester which was hydrolyzed as described in general procedure C yielding the title compound (28.5 mg, 100%). LC/MS (*m/z*) 464 (M+1)<sup>+</sup>.

#### Example 39

## 3-(Biphenyl-4-yl)-(2S)-[(3-hydroxy-napthalene-2-carbonyl)-amino]-propionic acid

The title compound (26 mg, 65%) was prepared from 0.05 g (0.1 mmol) of resin-bound 3-(4-bromophenyl)ethyl-(2S)-[3-(hydroxy-napthalene-2-carbonyl)-amino]-propionic acid methyl ester and 36.0 mg (0.3 mmol) of phenyl boronic acid as described in Example 38. LC/MS (*m/z*): 412 (*M*+1)<sup>+</sup>.

## Example 40

## (2S)-[(3-Hydroxy-napthalene-2-carbonyl)-amino]-3-[(3'-nitro)-biphenyl-4-yl]-propionic acid

The title compound (27 mg, 60%) was prepared from 0.05 g (0.1 mmol) of resin-bound 3-(4-bromophenyl)ethyl-(2S)-[3-(hydroxy-napthalene-2-carbonyl)-amino]-propionic acid methyl ester and 50.0 mg (0.3 mmol) of 3-nitro-phenyl boronic acid as described in Example 38. LC/MS (*m/z*): 457 (*M*+1)<sup>+</sup>.

## Example 41

## 3-(Biphenyl-4-yl)-(2S)-[(3'-chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester

To 1.0 g (2.5 mmol) of resin-bound 5-bromo-2-hydroxy-benzoic acid obtained by a similar procedure as in Example 37 were added 1.92 g (7.5 mmol) of (2S)-amino-3-biphenyl-4-yl-propionic acid methyl ester, 7.5 mL (7.5 mmol) of 1.0 *M* DIC in DMF, 7.5 mL (7.5 mmol) of 1.0 *M* HOBt in DMF, and a catalytic amount of DMAP. The resulting mixture was left on a shaker overnight. The resin was washed with DMF, MeOH, DCM three times of each to give resin-bound 3-(biphenyl-4-yl)-(2S)-(5-bromo-4-hydroxy-benzoylamino)-propionic acid methyl ester.

To 0.05 g (0.1 mmol) of above resin-bound 3-(biphenyl-4-yl)-(2S)-(5-bromo-4-hydroxy-benzoylamino)-propionic acid methyl ester in 2.0 mL of DME were added 52.0 mg (0.3 mmol) of 3-chloro-4-fluorophenylboronic acid, 30 mg (0.03 mmol) of Pd(PPh<sub>3</sub>)<sub>4</sub>, and 0.3 mL (0.6 mmol) of 2*N* Na<sub>2</sub>CO<sub>3</sub> solution. The mixture was heated to 80 °C for 12 h. The resin was washed with H<sub>2</sub>O, DMF, MeOH, DCM three times of each and cleaved with TMSBr/TFA/DCM (1:1:5) at rt for 4h. The residue obtained after removing the solvent was purified by chromatography (DCM) to give 35 mg (70%) of title compound LC/MS (*m/z*): 490 (*M*+1)<sup>+</sup>.

## Example 42

3-(Biphenyl-4-yl)-(2S)-[(4'-trifluoromethyl-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester

The resin-bound 3-(biphenyl-4-yl)-(2S)-(5-bromo-4-hydroxy-benzoyl-amino)-propionic acid methyl ester (50 mg, 0.1 mmol) obtained as in Example 37 was reacted with 4-trifluoromethyl phenyl boronic acid (56.7 mg, 0.3 mmol) as generally described in Example 41 to provide the title compound (36 mg, 70%) as a white solid. LC/MS (*m/z*): 520 (*M*+1)<sup>+</sup>.

#### Example 43

(2S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester

To 2.50 g (5.0 mmol) of resin-bound methyl 5-bromo-2-hydroxy-benzoate obtained by a similar procedure as in Example 37 in 30 mL of DME were added 2.60 g (15 mmol) of 3-chloro-4-fluorophenylboronic acid, 1.12 g (1.0 mmol) of Pd(PPh<sub>3</sub>)<sub>4</sub>, and 15 mL (30.0 mmol) of 2*N* Na<sub>2</sub>CO<sub>3</sub> solution. The mixture was heated to 80 °C for 12 h. The resin was washed with H<sub>2</sub>O, DMF, MeOH, DCM three times of each, and was hydrolyzed by LiOH/H<sub>2</sub>O/THF/ethanol at rt for 3 days to give the resin-bound 3'-chloro-4'-fluoro-4-hydroxy-biphenyl-3-carboxylic acid.

To 1.5 g (2.5 mmol) of above resin-bound 3'-chloro-4'-fluoro-4-hydroxy-biphenyl-3-carboxylic acid were added 1.95 g (7.5 mmol) of L-4-bromophenylalanine methyl ester, 7.5 mL (7.5 mmol) of 1.0 *M* DIC in DMF, 7.5 mL (7.5 mmol) of 1.0 *M* HOBt in DMF, and catalytic amount of DMAP. The resulting mixture was left on a shaker overnight. The resin was washed with DMF, MeOH, DCM three times of each to give resin-bound 3-(4-bromo-phenyl)-2-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester.

To 0.05 g (0.1 mmol) of above resin-bound 3-(4-bromo-phenyl)-(2S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester in 2.0 mL of DME were added 58.0 mg (0.3 mmol) of 3-(trifluoromethyl)phenylboronic acid, 30 mg (0.03 mmol) of Pd(PPh<sub>3</sub>)<sub>4</sub>, and 0.3 mL (0.6 mmol) of 2*N* Na<sub>2</sub>CO<sub>3</sub> solution. The mixture was heated at 80 °C for 12 h. The resin was washed with H<sub>2</sub>O, DMF, MeOH, DCM three times of each and cleaved with TMSBr/TFA/DCM (1:1:5) at rt for 4h. The residue obtained after removing the solvent was purified by chromatography (100% DCM) to give 29 mg (50%) of the title compound. LC/MS (*m/z*): 572 (*M*+1)<sup>+</sup>.

#### Example 44



3-(4'-Nitro-biphenyl-4-yl)-(2S)-[(4'-trifluoromethyl-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester

The resin-bound 3-(4-bromo-phenyl)-(2S)-[(4'-trifluoromethyl-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester (50 mg, 0.1 mmol) prepared as generally described in Example 37 was reacted with 4-nitro-phenyl boronic acid (50.1 mg, 0.3 mmol) by adapting the procedure as described in Example 43 to give title compound (28.2 mg, 50%). LC/MS (*m/z*): 565 (*M*+1)<sup>+</sup>.

#### Example 45

3-(3'-Trifluoromethyl-biphenyl-4-yl)-(2S)-[(4'-trifluoromethyl-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester

The resin-bound 3-(4-bromo-phenyl)-(2S)-[(4'-trifluoromethyl-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester (50 mg, 0.1 mmol) prepared as described in above Example 44 was reacted with 3-trifluoromethyl-phenyl boronic acid (57.2 mg, 0.3 mmol) by following as generally described in Example 44 to give title compound (29.2 mg, 50%). LC/MS (*m/z*): 588 (*M*+1)<sup>+</sup>.

#### Example 46

3-(4'-Trifluoromethyl-biphenyl-4-yl)-(2S)-[(4'-trifluoromethyl-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester

The resin-bound 3-(4-bromo-phenyl)-(2S)-[(4'-trifluoromethyl-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester (50 mg, 0.1 mmol) prepared as generally described in Example 37 was reacted with 4-trifluoromethyl-phenyl boronic acid (57.2 mg, 0.3 mmol) by adapting the procedure in Example 45 to give the title compound (29.2 mg, 50%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 3.30-3.42 (m, 2H), 3.84 (s, 3H), 5.11 (dd, 1H), 6.82 (d, 1H), 7.10 (d, 1H), 7.43-7.45 (m, 2H), 7.53-7.57 (m, 4H), 7.60-7.70 (m, 6H); LC/MS (*m/z*): 588 (*M*+1)<sup>+</sup>.

By analogous methods to those described above the following Examples were synthesized;

EXAMPLE	NAME	LC/MS ( <i>m/z</i> )

EXAMPLE	NAME	LC/MS (m/z)
47	3-Biphenyl-4-yl-(2S)-[(2',4'-difluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid	488
48	3-Biphenyl-4-yl-(2S)-[(4'-chloro-3'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	504
49	3-Biphenyl-4-yl-(2S)-[(3'-chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid	490
50	3-Biphenyl-4-yl-(2S)-[(4-hydroxy-3'-nitro-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	499
51	3-Biphenyl-4-yl-(2S)-[(4-hydroxy-4'-trifluoromethoxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	536
52	(2S)-[(4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(3'-nitro-biphenyl-4-yl)-propionic acid	553
53	(2S)-[(4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(3'-nitro-biphenyl-4-yl)-propionic acid methyl ester	566
54	(2S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-nitro-biphenyl-4-yl)-propionic acid methyl ester	551
55	3-Biphenyl-4-yl-(2S)-[(4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	470
56	3-Biphenyl-4-yl-(2S)-[(4-hydroxy-4'-methoxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	482

EXAMPLE	NAME	LC/MS (m/z)
57	3-Biphenyl-4-yl-(2S)-[(4'-tert-butyl-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	508
58	(2S)-[(4-Hydroxy-3'-nitro-biphenyl-3-carbonyl)-amino]-3-(3'-rifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester	567
59	3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-(2S)-[(4-hydroxy-3'-nitro-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	551
60	(2S)-[(4'-Amino-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-biphenyl-4-yl-propionic acid methyl ester	467
61	(2S)-[(3'-Amino-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-biphenyl-4-yl-propionic acid methyl ester	467
62	3-Biphenyl-4-yl-(2S)-[(5'-fluoro-4-hydroxy-2'-methoxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	500
63	3-Biphenyl-4-yl-(2S)-[(3'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	470
64	3-Biphenyl-4-yl-(2S)-[(4-hydroxy-3'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	520

EXAMPLE	NAME	LC/MS (m/z)
65	3-Biphenyl-4-yl-(2S)-[(4-hydroxy-3',5'-bis-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	588
66	3-Biphenyl-4-yl-(2S)-[(3'-chloro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	486
67	3-Biphenyl-4-yl-(2S)-[(4'-chloro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	486
68	3-Biphenyl-4-yl-(2S)-[(3',5'-difluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	488
69	3-Biphenyl-4-yl-(2S)-[(4'-fluoro-4-hydroxy-3'-methyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	483
70	(2S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester	572
71	(2S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(4'-methoxy-biphenyl-4-yl)-propionic acidmethyl ester	534
72	3-Biphenyl-4-yl-(2S)-[(4-hydroxy-4'-trifluoromethoxy-biphenyl-3-carbonyl)-amino]-propionic acid	522

EXAMPLE	NAME	LC/MS (m/z)
73	3-Biphenyl-4-yl-(2S)-[(4'-tert-butyl-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid	494
74	3-Biphenyl-4-yl-(2S)-[(4-hydroxy-3',4'-dimethoxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	512
75	(2S)-(5-Benzo[1,3]dioxol-5-yl-2-hydroxy-benzoylamino)-3-biphenyl-4-yl-propionic acid methyl ester	496
76	3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-(2S)-[(4-hydroxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	572
77	3-Biphenyl-4-yl-(2S)-[(4-hydroxy-4'-methanesulfonyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	530
78	(2S)-[(3'-Amino-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester	535
79	3-(3',5'-Bis-trifluoromethyl-biphenyl-4-yl)-(2S)-[(3'-chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	640
80	3-(3',5'-Bis-trifluoromethyl-biphenyl-4-yl)-(2S)-[(4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	606

EXAMPLE	NAME	LC/MS (m/z)
81	3-(3',5'-Bis-trifluoromethyl-biphenyl-4-yl)-(2S)-[[4-hydroxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	656
82	(2S)-[[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionic acid	558
83	(2S)-[[(4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethoxy-biphenyl-4-yl)-propionic acid methyl ester	604
84	(2S)-[[(4-Hydroxy-3'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester	588
85	4'-{[(2S)-[[(4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-2-methoxycarbonyl-ethyl]-5-nitro-biphenyl-3-carboxylic acid methyl ester	623
86	(2S)-[[(4-Hydroxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(3',4',5'-trimethoxy-biphenyl-4-yl)-propionic acid methyl ester	610
87	(2S)-[[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethoxy-biphenyl-4-yl)-propionic acid methyl ester	588
88	3-Biphenyl-4-yl-(2S)-[[(4-hydroxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid	506

EXAMPLE	NAME	LC/MS (m/z)
89	(2S)-[(4-Hydroxy-2'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(2'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester	588
90	3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-(2S)-[(3'-chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	556
91	(2S)-[(4-Hydroxy-3'-nitro-biphenyl-3-carbonyl)-amino]-3-(3'-nitro-biphenyl-4-yl)-propionic acid methyl ester	542
92	(2S)-[(4-Hydroxy-3'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(3'-nitro-biphenyl-4-yl)-propionic acid methyl ester	565
93	(2S)-[(4-Hydroxy-3'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester	588
94	3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-(2S)-[(4-hydroxy-3'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	572
95	3-Biphenyl-4-yl-(2S)-[(4-hydroxy-2'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	520
96	3-(3',5'-Bis-trifluoromethyl-biphenyl-4-yl)-(2S)-[(4-hydroxy-3'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester	656

EXAMPLE	NAME	LC/MS (m/z)
97	(2S)-[(4-Hydroxy-3'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(2'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester	588

## Example 98

(2S)-[2-(4-Benzoyloxy-benzyloxy)-5-bromo-benzoylamino]-3-biphenyl-4-yl-propionic acid  
 3-Biphenyl-4-yl-(2S)-(5-bromo-2-hydroxy-benzoylamino)-propionic acid methyl ester  
 (2.75 g, 35%) was prepared from (2S)-amino-3-biphenyl-4-yl-propionic acid methyl ester-  
 hydrochloride (5.0 g, 17.2 mmol), 5-bromo-2-hydroxy-benzoic acid (3.7 g, 17.2 mmol) as  
 described in general procedure A except for an adapted work-up. After reaction completion,  
 the reaction mixture was poured onto 150 mL of 1N HCl and 150 mL of EtOAc. The organic  
 layer was washed with 1N HCl, saturated sodium bicarbonate, dried over sodium sulfate and  
 evaporated. The crude material was purified over silica gel (7:3, DCM-hexanes).

(2S)-[2-(4-Benzoyloxy-benzyloxy)-5-bromo-benzoylamino]-3-biphenyl-4-yl-propionic  
 acid methyl ester (302 mg, 50%) was prepared from (2S)-3-Biphenyl-4-yl-2-(5-bromo-2-  
 hydroxy-benzoylamino)-propionic acid methyl ester (400 mg, 0.92 mmol) and 4-  
 benzyloxybenzyl chloride (256 mg, 0.39) as described in general procedure H and purified  
 over silica gel (8:2, DCM-hexanes).

(2S)-[2-(4-Benzoyloxy-benzyloxy)-5-bromo-benzoylamino]-3-biphenyl-4-yl-propionic  
 acid methyl ester (60 mg, 0.092 mmol) was dissolved in 5 mL of THF-MeOH (4-1), cooled to  
 0 °C and 1.1 equiv of 2 N LiOH added. After 30 minutes, 2.2 additional equiv of 2N LiOH  
 was added and the reaction stirred for 30 minutes. The reaction was worked up according to  
 general procedure C to give (2S)-[2-(4-Benzoyloxy-benzyloxy)-5-bromo-benzoylamino]-3-  
 biphenyl-4-yl-propionic acid (35 mg, 60%).

<sup>1</sup>H-NMR(400 MHz, DMSO-*d*<sub>6</sub>): 2.90 (m, 1H), 3.17 (m, 1H), 4.69 (m, 1H), 4.98 (s,  
 2H), 5.18 (s, 2H), 6.92 (m, 2H), 7.21 (m, 3H), 7.33 (m, 10H), 7.53 (d, 2H), 7.61 (m, 3H), 7.84  
 (d, 1H), 8.51(d, 1H); LC/MS (*m/z*): 638.1 (M+2)<sup>+</sup>.

## Example 99

3-Biphenyl-4-yl-(2S)-[4-(4-tert-butyl-benzyloxy)-3'-chloro-4'-fluoro-biphenyl-3-carbonyl]-  
 amino}-propionic acid



5-Bromo-2-(4-*t*-butyl-benzyloxy)-benzoic acid methyl ester (338 mg, 90%) was made from 5-bromosalicylic acid methyl ester (230 mg, 1.0 mmol) and *t*-butyl-benzyl bromide (226 mg, 1.0 mmol) following general procedure H, then hydrolyzed as in general procedure C to give the corresponding acid (310 mg, 95%). The above acid (40 mg, 0.11 mmol) was reacted with biphenyl alanine methyl ester (44 mg, 0.15 mmol) as described in general procedure A to give 3-biphenyl-4-yl-(2*S*)-[2-(4-*t*-butyl-benzyloxy)-5-bromo-benzoylamino] - propionic acid methyl ester. The methyl ester (60 mg, 0.1 mmol) so obtained was reacted with 3-chloro-4-fluorophenyl boronic acid (35 mg, 0.2 mmol) as described in general procedure D to provide the (2*S*)-[(3'-chloro-4'-fluoro-4-*tert*-butyl-benzyloxy - biphenyl-3-carbonyl)-amino]-3-biphenyl-4-yl-propionic acid methyl ester (52 mg, 80%). The ester was hydrolyzed following general procedure C to give the title compound (48 mg, 95%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 1.27 (s, 9H), 2.89 (m, 1H), 3.30 (m, 1H), 4.93 (m, 1H), 5.11 (m, 2H), 7.00 (m, 2H), 7.26-7.60 (m, 17H), 8.41(d, 1H), 8.58 (d, 1H); LC/MS (*m/z*): 636 (M+1)<sup>+</sup>.

#### 15 Example 100

(2*S*)-[5-Bromo-2-(4-trifluoromethylbenzyloxy)-benzoylamino]-3-(2'-phenoxybiphenyl-4-yl)-propionic acid

5-Bromo-salicylic acid (2.16 g, 10 mmol) was first transformed into 2-acetyl-5-bromo-salicylic acid (252 g, 98%) with acetyl chloride (2.34 g, 30 mmol) and pyridine (3.95 g, 50 mmol) in DCM. The above acid (1.29 g, 5.0 mmol) was converted into acid chloride by using oxyl chloride (1.97 g, 15 mmol) and catalytic amount of DMF in DCM, then 2-phenoxy-biphenyl alanine (1.45 g, 5.0 mmol) and DIEA (0.77 g, 6.0 mmol) were added to the acid chloride to form (2*S*)-[5-Bromo-2-hydroxybenzoylamino]-3-(2'-phenoxybiphenyl-4-yl)-propionic acid methyl ester (1.92 g, 85%). The above methyl ester (50 mg, 0.092 mmol) was reacted with 4-trifluoromethyl benzyl bromide (44 mg, 0.18 mmol) as described in general procedure H to provide (2*S*)-[5-Bromo-2-(4-trifluoromethylbenzyloxy)-benzoylamino]-3-(2'-phenoxybiphenyl-4-yl)-propionic acid methyl ester (55 mg, 85%). The ester was hydrolyzed following general procedure C to give the title compound (52 mg, 96%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 3.03, 3.22 (ABX, 2H), 4.92 (m, 3H), 6.64 (d, 1H), 6.76 (m, 2H), 6.85(dd, 1H), 6.93 (m, 2H), 7.00 (d, 2H), 7.07-7.24 (m, 7H), 7.39 (m, 4H), 8.22 (d, 1H), 8.26 (d, 1H); LC/MS (*m/z*): 690 (M+1)<sup>+</sup>.

#### 35 Example 101

(2*S*)-(5-Bromo-2-heptyloxy-benzoylamino)-3-[2'-(4-trifluoromethyl-phenoxy)-biphenyl-4-yl]-propionic acid

5-Bromo-2-heptyloxy-benzoic acid was prepared by reacting 5-bromo-2-hydroxy-benzoic acid methyl ester (1.0g, 4.32mmol) with iodoheptane (1.46g, 6.49mmol) as per general procedure H with potassium carbonate (1.5 g, 10.8mmol) added. The ester thus obtained was subjected to hydrolysis as per general procedure C to yield the 5-Bromo-2-heptyloxy-benzoic acid (0.950gm, 70%).

(2S)-Amino-3- (2'-hydroxy-biphenyl-4-yl)-propionic acid was prepared from 4-bromophenylalanine (5.0g, 20.48 mmol), 2-hydroxyphenylboronic acid (4.23g, 30.72mmol) and Pd (PPh<sub>3</sub>)<sub>4</sub> (2.36g, 2.038mmol) as per procedure D to yield the corresponding amino acid which was further esterified with methanolic solution of anhydrous HCl to yield the corresponding HCl salt of the (2S)-Amino-3- (2'-hydroxy-biphenyl-4-yl)-propionic acid methyl ester (5.0 g, 90% crude yield).

5-Bromo-2-heptyloxy-benzoic acid (0.231g, 0.738mmol) and the (2S)-amino-3- (2'-hydroxy-biphenyl-4-yl)-propionic acid methyl ester (0.200g, 0.738mmol) were then combined as per general procedure A with HBTU (0.335g, 0.885mmol) and diisopropylethylamine (0.285g, 2.21mmol) to yield the (2S)-(5-bromo-2-heptyloxy-benzoylamino)-3-(2'-hydroxy-biphenyl-4-yl)-propionic acid methyl ester (0.200g, 50%).

The title compound was prepared from (2S)-(5-bromo-2-heptyloxy-benzoylamino)-3-(2'-hydroxy-biphenyl-4-yl)-propionic acid methyl ester (0.080g, 0.140mmol) and 4-trifluoromethylphenylboronic acid (0.050g, 0.281mmol) as per general procedure G to give (2S)-(5-bromo-2-heptyloxy-benzoylamino)-3-[2'-(4-trifluoromethyl-phenoxy)-biphenyl-4-yl]-propionic acid methyl ester which was further hydrolyzed as per general procedure C to give the title compound (0.020g, 30% yield). <sup>1</sup>H-NMR(400 MHz, CDCl<sub>3</sub>): 1.14(t, 3H), 1.53 (m, 8H), 1.92(m, 2H), 3.6(m, 2H), 4.21(m, 2H), 5.21(m, 1H), 7.12(d, 1H), 7.22(m, 2H), 7.36(d, 1H), 7.5(d, 2H), 7.58(m, 2H), 7.66(m, 1H), 7.78 (m, 6H), 8.62 (s, 1H), 8.9 (bs, 1H). LC/MS (m/z): 700.2(M+2).

#### Example 102

2S-(5-Chloro-2-heptyloxy-benzoylamino)-3-(4'-trifluoromethoxy-biphenyl-4-yl)-propionic acid

5-Chloro-2-hydroxy-benzoic acid (2.5g, 28.97mmol) was coupled with 2-amino-3- (4-bromo-phenyl)-propionic acid methyl ester hydrochloride (4.26 g, 28.96 mmol) with HBTU (6.59 g, 34.76mmol) and diisopropylethylamine (8 ml, 86.91mmol) as per general procedure A to yield the corresponding 3-(4-Bromo-phenyl)-(2S)-(5-chloro-2-hydroxy-benzoylamino)-propionic acid methyl ester in 50% yield.

The above hydroxy compound (0.500 g, 1.21 mmol) was then alkylated with heptyliodide (0.410 g, 1.815 mmol) and potassium carbonate (0.050 g, 3.025 mmol) as per general procedure H to yield the 3-(4-bromo-phenyl)-(2S)-(5-chloro-2-heptyloxy-benzoylamino)-propionic acid methyl ester (0.500g, 80%)

- 5 The title compound was then prepared from 3-(4-bromo-phenyl)-(2S)-(5-chloro-2-heptyloxy-benzoylamino)-propionic acid methyl ester (0.090g, 0.176mmol) and trifluoromethyl boronic acid (0.067g, 0.352mmol) with Pd (PPh<sub>3</sub>) (0.020g, 0.0176mmol) and 2 N Na<sub>2</sub>CO<sub>3</sub> (0.528ml, 0.528mmol) as per general procedure D to yield the (2S)-(5-chloro-2-heptyloxy-benzoylamino)-3-(4'-trifluoromethoxy-biphenyl-4-yl)-propionic acid methyl ester
- 10 which was further hydrolyzed as per general procedure C to give the title compound (0.050 g, 50%)%. <sup>1</sup>H-NMR(400 MHz, CDCl<sub>3</sub>): 1.11(t, 3H), 1.44(m, 8H), 1.87(m, 2H), 3.65(dddd, 2H), 4.27(m, 2H), 5.50( m, 1H), 7.18( m, 2H), 7.4(d, 1H), 7.57(m, 4H), 7.68-7.85(m, 4H), 8.52 (s, 1H), 8.98 (bs, 1H). LC/MS (m/z): 578.2(M+2).

- 15 By analogous methods to those described above the following compounds were synthesized.

EXAMPLE	NAME	LC/MS (m/z)
103	3-Biphenyl-4-yl-(2S)-[2-(3,4-bis-benzyloxy-benzyloxy)-5-bromo-benzoylamino]-propionic acid methyl ester	757
104	3-Biphenyl-4-yl-(2S)-[2-(3,4-bis-benzyloxy benzyloxy)-5-bromo-benzoylamino]-propionic acid	743
105	(2S)-[2-(4-Benzyloxybenzyloxy)-5-bromo benzoylamino]-3-biphenyl-4-yl-propionic acid methyl ester	651
106	3-Biphenyl-4-yl-(2S)-[5-bromo-2-(4-bromo-benzyloxy)-benzoylamino]-propionic acid methyl ester	624

EXAMPLE	NAME	LC/MS (m/z)
107	3-Biphenyl-4-yl-(2S)-[5-bromo-2-(4-bromo-benzyloxy)-benzoylamino]-propionic acid	610
108	3-Biphenyl-4-yl-(2S)-[5-bromo-2-(4-tert-butyl-benzyloxy)-benzoylamino]-propionic acid methyl ester	601
109	3-Biphenyl-4-yl-(2S)-[5-bromo-2-(4-tert-butyl-benzyloxy)-benzoylamino]-propionic acid	587
110	3-Biphenyl-4-yl-(2S)-[2-(biphenyl-4-ylmethoxy)-5-bromo-benzoylamino]-propionic acid	607
111	3-Biphenyl-4-yl-(2S)-(5-chloro-2-methoxy-benzoyl amino)-propionic acid	410
112	3-Biphenyl-4-yl-(2S)-[2-(4-tert-butyl-benzyloxy)-5-chloro-benzoylamino]-propionic acid	542
113	3-Biphenyl-4-yl-(2S)-[2-(4-tert-butyl-benzyloxy)-5-(4-trifluoromethylphenyl)-benzoylamino]-propionic acid	636
114	(2S)-[5-Bromo-2-(3-methyl-benzyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	652

EXAMPLE	NAME	LC/MS (m/z)
115	(2S)-[5-Bromo-2-(4-methyl-benzyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	637
116	(2S)-[5-Bromo-2-(3-methyl-benzyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	637
117	(2S)-[5-Bromo-2-(4-carboxy-benzyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	667
118	(2S)-[5-Bromo-2-(4-trifluoromethyl-phenoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	677
119	(2S)-(5-Bromo-2-heptyloxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	645
120	3-Biphenyl-4-yl-(2S)-(5-bromo-2-heptyloxy-benzoylamino)-propionic acid methyl ester	553
121	3-Biphenyl-4-yl-(2S)-(5-bromo-2-heptyloxy-benzoylamino)-propionic acid	539

EXAMPLE	NAME	LC/MS (m/z)
122	(2S)-(5-Bromo-2-heptyloxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	631
123	3-Biphenyl-4-yl-(2S)-[5-chloro-2-(4-pyrazol-1-yl-benzyloxy)-benzoylamino]-propionic acid	552
124	(2S)-[5-Bromo-2-(4-tert-butyl-benzyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	679
125	(2S)-(2-Benzyloxy-5-bromo-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	637
126	(2S)-(2-Benzyloxy-5-bromo-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	623
127	(2S)-[5-Bromo-2-(4-bromo-benzyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	702
128	(2S)-(5-Bromo-2-propoxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	575
129	(2S)-[(5-Bromo-2,3-dihydro-benzofuran-7-carbonyl)-amino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	559

EXAMPLE	NAME	LC/MS (m/z)
130	(2S)-[5-Bromo-2-(3-phenyl-allyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	663
131	(2S)-[5-Bromo-2-(3-phenyl-allyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	649
132	(2S)-[5-Bromo-2-(4-methanesulfonyl-benzyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	715
133	(2S)-[5-Bromo-2-(4-methanesulfonyl-benzyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	701
134	(2S)-[5-Bromo-2-(3-methyl-butoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	617
135	(2S)-[5-Bromo-2-(3-methyl-butoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	603
136	(2S)-[2-(Biphenyl-4-ylmethoxy)-5-bromo-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	713
137	(2S)-[2-(Biphenyl-4-ylmethoxy)-5-bromo-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	699

EXAMPLE	NAME	LC/MS (m/z)
138	(2S)-[5-Bromo-2-(4-methoxy-phenoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	639
139	(2S)-[5-Bromo-2-(4-phenoxy-benzyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	715
140	(2S)-[5-Bromo-2-(1-methyl-butoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	617
141	(2S)-[5-Bromo-2-(1-methyl-butoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	603
142	(2S)-[5-Bromo-2-isopropoxy-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	575
143	(2S)-[5-Bromo-2-(3-trifluoromethyl-phenoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	677
144	(2S)-[5-Bromo-2-heptyloxy-benzoylamino]-3-[2'-(4-methoxy-phenoxy)-biphenyl-4-yl]-propionic acid	661
145	(2S)-[5-Bromo-2-(2-morpholin-4-yl-ethoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	660



EXAMPLE	NAME	LC/MS (m/z)
146	(2S)-{5-Bromo-2-[2-(2-methoxy-ethoxy)-ethoxy]-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	649
147	(2S)-(5-Bromo-2-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	693
148	(2S)-(5-Bromo-2-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	658
149	(2S)-{5-Bromo-2-[2-(2-oxo-pyrrolidin-1-yl)-ethoxy]-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	658
150	(2S)-[5-Bromo-2-(2-phenyl-cyclopropylmethoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	663
151	(2S)-(5-Bromo-2-sec-butoxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	589
152	(2S)-(5-Chloro-2-heptyloxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	600
153	(2S)-(5-Chloro-2-heptyloxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	586

EXAMPLE	NAME	LC/MS (m/z)
154	(2S)-(5-Bromo-2-isobutoxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	603
155	(2S)-(5-Bromo-2-isobutoxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	588
156	(2S)-(5-Bromo-2-ethoxycarbonyloxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	619
157	(2S)-(5-Bromo-2-dimethylcarbamoyloxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	618
158	(2S)-[5-Bromo-2-[2-(2-methoxy-ethoxy)-ethoxy]-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	635
159	(2S)[5-Bromo-2-(4-phenyl-butoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	665
160	(2S)-[5-Bromo-2-(5-phenyl-pentyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	679
161	(2S)-[5-Bromo-2-(6-phenyl-hexyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	693

EXAMPLE	NAME	LC/MS (m/z)
162	(2S)-(5-Bromo-2-heptyloxy-benzoylamino)-3-[2'-(4-trifluoromethoxy-phenoxy)-biphenyl-4-yl]-propionic acid	715
163	(2S)-(5-Bromo-2-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	679
164	(2S)-[5-Bromo-2-(2-piperidin-1-yl-ethoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	644
165	(2S)-(5-Bromo-2-heptyloxy-benzoylamino)-3-[2'-(4-tert-butyl-phenoxy)-biphenyl-4-yl]-propionic acid	687
166	(2S)-(5-Chloro-2-heptyloxy-benzoylamino)-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid	562
167	3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-(2S)-(5-chloro-2-heptyloxy-benzoylamino)-propionic acid	546
168	(2S)-[5-Bromo-2-(3-phenyl-propoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	651
169	(2S)-(5-Bromo-2-[3-(3,4-dimethoxy-phenyl)-propoxy]-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	711

EXAMPLE	NAME	LC/MS (m/z)
170	(2S)-[5-Bromo-2-(3-pyridin-3-yl-propoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	652
171	(2S)-[5-Bromo-2-(3-pyridin-4-yl-propoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	652
172	(2S)-(5-Bromo-2-dimethylcarbamoyloxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	604
173	(2S)-[5-Bromo-2-(3-morpholin-4-yl-propoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	660
174	(2S)-[5-Bromo-2-(4,4,4-trifluoro-butoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	643
175	(2S)-(5-Chloro-2-heptyloxy-benzoylamino)-3-(4'-cyclohexyl-biphenyl-4-yl)-propionic acid	576
176	(2S)-(5-Chloro-2-heptyloxy-benzoylamino)-3-(3',4'-dichloro-biphenyl-4-yl)-propionic acid	562
177	(2S)-(5-Bromo-2-butoxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	589

EXAMPLE	NAME	LC/MS (m/z)
178	(2S)-[5-Bromo-2-(2-methyl-butoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	603
179	(2S)-(5-Bromo-2-cyclopropylmethoxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	601
180	(2S)-(5-Bromo-2-cyclopropylmethoxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	587
181	(2S)-[5-Bromo-2-(4-[1,2,4]triazol-1-yl-benzyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	690
182	(2S)-[5-Bromo-2-(isoquinolin-1-ylmethoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	674
183	(2S)-[2-(3-Benzyloxy-benzyloxy)-5-bromo-benzoylamino]-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	743
184	(2S)-[2-(3-Benzyloxy-benzyloxy)-5-bromo-benzoylamino]-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid	728
185	(2S)-[5-Bromo-2-(4-trifluoromethoxy-benzyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	721

EXAMPLE	NAME	LC/MS (m/z)
186	(2S)-[5-Bromo-2-(4-trifluoromethoxy-benzyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	707
187	(2S)-[5-Bromo-2-(4-phenyl-butoxy)-benzoylamino]-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	679
188	(2S)-[5-Bromo-2-(6-phenyl-hexyloxy)-benzoylamino]-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	707
189	(2S)-[5-Chloro-2-heptyloxy-benzoylamino]-3-(4'-dimethylamino-biphenyl-4-yl)-propionic acid	537
190	(2S)-[5-Bromo-2-(4-phenyl-butoxy)-benzoylamino]-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid	665
191	(2S)-[5-Bromo-2-(6-phenyl-hexyloxy)-benzoylamino]-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid	693
192	(2S)-[5-Bromo-2-(2-cyclohexyl-ethoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	657
193	(2S)-[5-Bromo-2-(2-cyclohexyl-ethoxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	643

EXAMPLE	NAME	LC/MS (m/z)
1944	(2S)-(5-Bromo-2-cyclohexylmethoxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	629
195	(2S)-(5-Bromo-2-cyclohexyloxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	629
196	(2S)-(5-Bromo-2-cyclohexyloxy-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	615

## Example 197

*N*-[2-Hydroxy-4-(4-trifluoromethyl-phenoxy)-phenyl]-2-(3'-methoxy-biphenyl-4-yl)-acetamide

5 To 4.0 g (4.0 mmol) of resin-bound 5-fluoro-2-nitro-phenol obtained by a similar procedure as in Example 37 in 8.0 mL of DMF were added 1.31 g (8.0 mmol) of 4-hydroxybenzotrifluoride, and 1.20 g (8.0 mmol) of K<sub>2</sub>CO<sub>3</sub>. The mixture was heated to 110 °C for 12 h. The resin was washed with H<sub>2</sub>O, DMF, MeOH, DCM three times of each, and was reduced by SnCl<sub>2</sub> hydrate in NMP at rt for 4h to give the resin-bound 2-amino-5-(4-trifluoromethyl-phenoxy)-phenol.

10 To 3.0 g (2.5 mmol) of above resin-bound 2-amino-5-(4-trifluoromethyl-phenoxy)-phenol were added 1.62 g (7.5 mmol) of 4-bromophenylacetic acid, 7.5 mL (7.5 mmol) of 1.0 M DIC in DMF, 7.5 mL (7.5 mmol) of 1.0 M HOBT in DMF, and a catalytic amount of DMAP. The resulting mixture was left on a shaker overnight. The resin was washed with DMF, 15 MeOH, DCM three times of each to give resin-bound 2-(4-bromo-phenyl)-*N*-[2-Hydroxy-4-(4-trifluoromethyl-phenoxy)-phenyl]-acetamide.

20 To 120 mg (0.1 mmol) of above resin-bound 2-(4-bromo-phenyl)-*N*-[2-Hydroxy-4-(4-trifluoromethyl-phenoxy)-phenyl]-acetamide in 2.0 mL of DME were added 46.0 mg (0.3 mmol) of 3-methoxyphenylboronic acid, 30 mg (0.03 mmol) of Pd(PPh<sub>3</sub>)<sub>4</sub>, and 0.3 mL (0.6 mmol) of 2N Na<sub>2</sub>CO<sub>3</sub> solution. The mixture was heated to 80 °C for 12 h. The resin was washed with H<sub>2</sub>O, DMF, MeOH, DCM three times of each and cleaved with TMSBr/TFA/DCM (1:1:5) at rt for 4h. The residue obtained after removing the solvent was

purified by chromatography (100% methylene chloride) to give 25 mg (50%) of the title compound. LC/MS ( $m/z$ ) 494 ( $M+1$ )<sup>+</sup>.

Example 198

5

*N*-[2-Hydroxy-4-(3,4-dichloro-phenoxy)-phenyl]-2-(4'-trifluoromethyl-biphenyl-4-yl)-acetamide

The resin-bound 2-(4-bromo-phenyl)-*N*-[2-Hydroxy-4-(3,4-dichloro-phenoxy)-phenyl]-acetamide (120 mg, 0.1 mmol) prepared as described in Example 197 was reacted with 4-trifluoromethyl-phenyl boronic acid (56.7mg, 0.3 mmol) as generally described in Example 10 197 to afford (26.9 mg, 50%) the title compound.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 3.88 (s, 2H), 6.48 (dd, 1H), 6.66 (d, 1H), 6.79-6.85 (m, 2H), 7.05 (d, 1H), 7.36 (d, 2H), 7.46-7.48 (m, 2H), 7.66-7.68 (m, 2H), 7.71 (m, 4H), 8.92 (s, 1H); LC/MS ( $m/z$ ): 532 ( $M+1$ )<sup>+</sup>.

Example 199

15

*N*-[2-Hydroxy-4-(2,4-dichloro-6-methyl-phenoxy)-phenyl]-2-(4'-trifluoromethyl-biphenyl-4-yl)-acetamide

The resin-bound 2-(4-bromo-phenyl)-*N*-[2-Hydroxy-4-(3,4-dichloro-6-methyl-phenoxy)-phenyl]-acetamide (120 mg, 0.1 mmol) prepared as described in Example 197 was reacted with 4-trifluoromethyl-phenyl boronic acid (56.7mg, 0.3 mmol) as generally 20 described in Example 197 to afford (27.5 mg, 50%) of title compound.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 2.13 (s, 3H), 3.86 (s, 2H), 6.33 (dd, 1H), 6.36 (d, 1H), 6.69 (d, 1H), 7.15 (d, 1H), 7.29 (d, 1H), 7.45 (d, 2H), 7.64-7.71 (m, 6H), 8.92 (s, 1H); LC/MS ( $m/z$ ): 546 ( $M+1$ )<sup>+</sup>.

25

Example 200

*N*-[2-Hydroxy-4-(2,4-dichloro-6-methyl-phenoxy)-phenyl]-2-(3'-trifluoromethyl-biphenyl-4-yl)-acetamide

30

The resin-bound 2-(4-bromo-phenyl)-*N*-[2-Hydroxy-4-(3,4-dichloro-6-methyl-phenoxy)-phenyl]-acetamide (120 mg, 0.1 mmol) prepared as described in Example 197 was reacted with 3-trifluoromethyl-phenyl boronic acid (56.7mg, 0.3 mmol) as generally described in Example 197 to afford (27.5 mg, 50%) of title compound.

35

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 2.13 (s, 1H), 3.86 (s, 2H), 6.33 (dd, 1H), 6.37 (d, 1H), 6.69 (d, 1H), 7.15 (m, 1H), 7.30 (d, 1H), 7.45 (dd, 2H), 7.59-7.65 (m, 4H), 7.78 (m, 1H), 7.84 (s, 1H), 8.84 (s, 1H); LC/MS ( $m/z$ ): 546 ( $M+1$ )<sup>+</sup>.



By analogous methods to those described above the following compounds were synthesized

EXAMPLE	NAME	LC/MS (m/z)
201	3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-N-[4-(2,4-dichloro-6-methyl-phenoxy)-2-hydroxy-phenyl]-propionamide	544
202	N-[4-(2-Fluoro-6-methoxy-phenoxy)-2-hydroxy-phenyl]-3-(3'-methoxy-biphenyl-4-yl)-propionamide	488
203	N-[4-(2,4-Dichloro-6-methyl-phenoxy)-2-hydroxy-phenyl]-2-(4'-methoxy-biphenyl-4-yl)-acetamide	508
204	2-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-N-[4-(2,4-dichloro-6-methyl-phenoxy)-2-hydroxy-phenyl]-acetamide	530
205	2-Biphenyl-4-yl-N-[2-hydroxy-4-(4'-methoxy-biphenyl-4-yloxy)-phenyl]-acetamide	502
206	2-Biphenyl-4-yl-N-[2-hydroxy-4-(4'-trifluoromethyl-biphenyl-4-yloxy)-phenyl]-acetamide	540
207	N-[4-(3,4-Dichloro-phenoxy)-2-hydroxy-phenyl]-2-(3'-nitro-biphenyl-4-yl)-acetamide	508

# 5 Example 208

*N*-[5-(3-Chloro-phenyl)-pyridin-2-yl]-2-[4-(3-hydroxy-4-nitro-phenoxy)-phenyl]-acetamide

To 4.0 g (4.0 mmol) of resin-bound 5-fluoro-2-nitro-phenol prepared as generally described in Example 37 in 8.0 mL of DMF were added 1.34 g (8.0 mmol) of methyl 4-hydroxyphenylacetate, and 1.20 g (8.0 mmol) of K<sub>2</sub>CO<sub>3</sub>. The mixture was heated to 110 °C for 12 h. The resin was washed with H<sub>2</sub>O, DMF, MeOH, DCM three times of each, and was

hydrolyzed by LiOH/H<sub>2</sub>O/THF/ethanol at rt for 12 h to give the resin-bound [4-(3-hydroxy-4-nitro-phenoxy)-phenyl]-acetic acid.

To 3.0 g (2.5 mmol) of above resin-bound [4-(3-hydroxy-4-nitro-phenoxy)-phenyl]-acetic acid were added 1.30 g (7.5 mmol) of 2-amino-5-bromopyridine, 7.5 mL (7.5 mmol) of 1.0 M DIC in DMF, 7.5 mL (7.5 mmol) of 1.0 M HOBt in DMF, and catalytic amount of DMAP. The resulting mixture was left on a shaker overnight. The resin was washed with DMF, MeOH, DCM three times of each to give resin-bound *N*-(5-bromo-pyridin-2-yl)-2-[4-(3-hydroxy-4-nitro-phenoxy)-phenyl]-acetamide

To 120 mg (0.1 mmol) of above resin-bound bound *N*-(5-bromo-pyridin-2-yl)-2-[4-(3-hydroxy-4-nitro-phenoxy)-phenyl]-acetamide in 2.0 mL of DME were added 48.0 mg (0.3 mmol) of 3-chlorophenylboronic acid, 30 mg (0.03 mmol) of Pd(PPh<sub>3</sub>)<sub>4</sub>, and 0.3 mL (0.6 mmol) of 2*N* Na<sub>2</sub>CO<sub>3</sub> solution. The mixture was heated to 80 °C for 12 h. The resin was washed with H<sub>2</sub>O, DMF, MeOH, DCM three times of each and cleaved with TMSBr/TFA/DCM (1:1:5) at rt for 4h. The residue obtained after removing the solvent was purified by chromatography (silica gel, DCM) to give 20 mg (40%) of the title compound.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 3.81 (s, 2H), 6.51-6.55 (m, 1H), 6.60–6.63 (m, 1H), 7.11-7.13 (m, 2H), 7.26-7.45 (m, 5H), 7.52 (m, 1H), 7.91 (dd, 1H), 8.08 (m, 1H), 8.34 (d, 1H), 8.43 (m, 1H), 10.89 (s, 1H); LC/MS (*m/z*): 476 (M+1)<sup>+</sup>.

#### Example 209

*N*-[5-(3,4-Dichloro-phenyl)-pyridin-2-yl]-2-[4-(3-hydroxy-4-nitro-phenoxy)-phenyl]-acetamide

The resin-bound *N*-(5-bromo-pyridin-2-yl)-2-[4-(3-hydroxy-4-nitro-phenoxy)-phenyl]-acetamide (120 mg, 0.1 mmol) was reacted with 3,4-dichloro-phenyl boronic acid (57 mg, 0.3 mmol) as described in example 208 to afford 25 mg (45%) of the title compound. LC/MS (*m/z*): 510 (M+1)<sup>+</sup>.

#### Example 210

*N*-[5-(3-Trifluoromethyl-phenyl)-pyridin-2-yl]-2-[4-(3-hydroxy-4-nitro-phenoxy)-phenyl]-acetamide

The resin-bound *N*-(5-bromo-pyridin-2-yl)-2-[4-(3-hydroxy-4-nitro-phenoxy)-phenyl]-acetamide (120 mg, 0.1 mmol) was reacted with 3-trifluoromethyl-phenyl boronic acid (57 mg, 0.3 mmol) as described in example 208 to afford 22.9 mg (45%) of the title compound.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 3.72 (s, 2H), 3.89 (s, 3H), 6.52 (m, 1H), 6.58-6.63 (m, 1H), 7.07-7.11 (m, 2H), 7.48-7.50 (m, 2H), 7.66-7.78 (m, 4H), 8.06-8.09 (m, 1H), 8.25 (dd, 1H), 8.43 (dd, 1H), 8.72 (d, 1H), 10.90 (s, 1H); LC/MS (*m/z*): 510 (M+1)<sup>+</sup>.

5      Example 211

*N*-[5-(4-Methoxy-phenyl)-pyridin-2-yl]-2-[4-(3-hydroxy-4-nitro-phenoxy)-phenyl]-acetamide

The resin-bound *N*-(5-bromo-pyridin-2-yl)-2-[4-(3-hydroxy-4-nitro-phenoxy)-phenyl]-acetamide (120 mg, 0.1 mmol) was reacted with 4-methoxy-phenyl boronic acid (45 mg, 0.3 mmol) as described in example 208 to afford 21.2 mg (45%) of the title compound.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 3.87 (s, 3H), 3.88 (s, 2H), 6.52 (d, 1H), 6.61 (dd, 1H), 7.01-7.03 (m, 2H), 7.08-7.10 (m, 2H), 7.46-7.50 (m, 4H), 8.08 (d, 1H), 8.16 (dd, 1H), 8.36 (dd, 1H), 8.62 (d, 1H), 10.89 (s, 1H); LC/MS (*m/z*): 472 (M+1)<sup>+</sup>.

15      Example 212

3-Biphenyl-4-yl-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid

(2S)-Amino-3-biphenyl-4-yl-propionic acid methyl ester (1.0g mg, 4.1 mmol) was reacted with 4-bromo-benzoic acid (1.07g mg, 5.3 mmol) as described in general procedure A yielding 3-biphenyl-4-yl-(2S)-[(5-bromo-benzoyl-amino)-propionic acid (1.48g, 85%).

3-Biphenyl-4-yl-(2S)-[(5-bromo-benzoylamino)-propionic acid (100mg, 0.23 mmol) was reacted with 4-trifluoromethyl phenyl boronic acid (0.133 mg, 0.69 mmol) by following general procedure D yielding the title compound (98 mg, 85%) as a white solid.

<sup>1</sup>H-NMR(400 MHz, DMSO-*d*<sub>6</sub>): 3.07-3.25(m, 2H), 4.63-4.69 (m, 1H), 7.26-7.32 (m, 1H), 7.39-7.42 (m, 4H), 7.56-7.62 (m, 4H), 7.1-7.84 (m, 4H), 7.81-7.84 (m, 4H), 7.92-7.95 (m, 4H), 8.86 (d, 1H); LC/MS (*m/z*): 490 (M+1)<sup>+</sup>.

Example 213

30      3-Biphenyl-4-yl-(2S)-[(3'-chloro-4'-fluoro-biphenyl-4-carbonyl)-amino]-propionic acid

3-Biphenyl-4-yl-(2S)-[(5-bromo-benzoyl-amino)-propionic acid (100mg, 0.23 mmol) was reacted with 3-chloro-4-fluoro-phenyl boronic acid (0.123 mg, 0.69 mmol) by following general procedure D to afford title compound (89 mg, 80%) as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>COCD<sub>3</sub>): 4.05 (dd, 2H), 5.00 (m, 1H), 7.32 (m, 1H), 7.44 (m, 4H), 7.62 (m, 4H), 7.71 (m, 1H), 7.74 (m, 2H), 7.84 (m, 1H), 7.96 (m, 3H). LC/MS (*m/z*): 474 (M+1)<sup>+</sup>.

## Example 214

3-Biphenyl-4-yl-(2S)-[(4'-trifluoromethoxy-biphenyl-4-carbonyl)-amino]-propionic acid

5        3-Biphenyl-4-yl-(2S)-[(5-bromo-benzoyl-amino)-propionic acid (100 mg, 0.23 mmol)  
was reacted with 4-trifluoromethoxyphenylboronic acid (0.145 mg, 0.69 mmol) by following  
general procedure D yielding the title compound (101 mg, 85%) as a white solid:

$^1\text{H-NMR}$ (400 MHz,  $\text{DMSO-}d_6$ ): 3.08-3.15 (m, 1H), 3.20-3.25 (m, 1H), 4.62-4.68 (m,  
1H), 7.28-7.32 (m, 1H), 7.39-7.46 (m, 6H), 7.55-7.61 (m, 4H), 7.77 (d, 2H), 7.82 (d, 2H),  
7.92 (d, 2H), 8.84 (d, 1H); LC/MS ( $m/z$ ): 524 ( $M+1$ ) $^+$ .

10

## Example 215

3-Biphenyl-4-yl-(2S)-[(4'-ethyl-biphenyl-4-carbonyl)-amino]-propionic acid

15        3-Biphenyl-4-yl-(2S)-[(5-bromo-benzoyl-amino)-propionic acid (100 mg, 0.23 mmol)  
was reacted with 4-ethyl phenyl boronic acid (0.145 mg, 0.69 mmol) by following general  
procedure D yielding the title compound (101 mg, 85%) as a white solid. LC/MS ( $m/z$ ): 450  
( $M+1$ ) $^+$ .

## Example 216

20

3-Biphenyl-4-yl-(2S)-[(3'-ethyl-biphenyl-3-carbonyl)-amino]-propionic acid

(2S)-amino-3-biphenyl-4-yl-propionic acid methyl ester (1.0g mg, 4.1 mmol) was  
reacted with 3-bromo-benzoic acid (1.07g mg, 5.3 mmol) as described in general procedure  
A yielding 3-biphenyl-4-yl-(2S)-(3-bromo-benzoylamino)-propionic acid (1.48g, 85%).

25        3-Biphenyl-4-yl-(2S)-[(3-bromo-benzoyl-amino)-propionic acid (100mg, 0.23 mmol)  
was reacted with 4-ethyl phenyl boronic acid (0.145 mg, 0.69 mmol) by following general  
procedure D yielding the title compound (101 mg, 85%) as a white solid.

$^1\text{H-NMR}$ (400 MHz,  $\text{DMSO-}d_6$ ): 1.22 (t, 3H), 2.61 (q, 2H), 3.25-3.30 (m, 1H), 3.37-3.39  
(m, 1H), 5.06-5.08 (m, 1H), 6.75 (d, 1H,  $J = 6.4$  Hz), 7.15 (d, 2H), 7.24-7.26 (m, 2H), 7.30-  
30        7.33 (m, 1H), 7.36-7.43 (m, 5H), 7.49 (t, 4H), 7.60 (d, 1H), 7.64 (d, 1H), 7.85 (s, 1H); LC/MS  
( $m/z$ ): 450 ( $M+1$ ) $^+$ .

## Example 217

35        3-Biphenyl-4-yl-(2S)-[(4'-*tert*-butyl-biphenyl-3-carbonyl)-amino]-propionic acid

3-Biphenyl-4-yl-(2S)-[(3-bromo-benzoyl-amino)-propionic acid (100mg, 0.23 mmol) was reacted with 4-*tert*-butyl phenyl boronic acid (0.125 mg, 0.69 mmol) by following general procedure D yielding the title compound (95 mg, 85%) as a white solid.

<sup>1</sup>H-NMR(400 MHz, DMSO-*d*<sub>6</sub>): 1.31 (s, 9H), 3.34-3.42 (m, 1H), 3.42-3.46 (m, 1H), 5.10-5.14 (m, 1H), 6.62 (bs, 1H), 7.25 (s, 1H), 7.28 (d, 1H), 7.31-7.35 (m, 1H), 7.37-7.43 (m, 4H), 7.44-7.49 (m, 3H), 7.52-7.56 (m, 4H), 7.64 (d, 1H), 7.70-7.72 (m, 1H), 7.4 (s, 1H); LC/MS (*m/z*): 478 (M+1)<sup>+</sup>.

#### Example 218

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3-Biphenyl-4-yl-(2S)-[(4'-methoxy-biphenyl-3-carbonyl)-amino]-propionic acid

3-Biphenyl-4-yl-(2S)-[(3-bromo-benzoyl-amino)-propionic acid (100 mg, 0.23 mmol) was reacted with 4-methoxy-phenyl boronic acid (0.106 mg, 0.69 mmol) by following general procedure D yielding the title compound (85 mg, 80%) as a white solid.

<sup>1</sup>H-NMR(400 MHz, DMSO-*d*<sub>6</sub>): 3.26-3.31 (m, 1H), 3.39-3.40 (m, 1H), 3.77 (s, 3H), 5.02-5.04 (m, 1H), 6.73 (bs, 1H), 6.85 (d, 1H), 7.79 (m, 17H); LC/MS (*m/z*): 452 (M+1)<sup>+</sup>.

#### Example 219

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3-Biphenyl-4-yl-(2S)-[(4'-methane-sulfonyl-biphenyl-3-carbonyl)-amino]-propionic acid

3-Biphenyl-4-yl-(2S)-[(3-bromo-benzoyl-amino)-propionic acid (100mg, 0.23 mmol) was reacted with 4-methanesulfonyl-phenyl boronic acid (0.141 mg, 0.69 mmol) by following general procedure D yielding the title compound (102 mg, 87%) as a light yellow solid.

<sup>1</sup>H-NMR(400 MHz, CDCl<sub>3</sub>): 3.11-3.17 (m, 1H), 3.26-3.30 (m, 1H), 4.69-4.74 (m, 1H), 7.30-7.34 (m, 1H), 7.58-7.63 (m, 5H), 7.87-7.93 (m, 2H), 7.98-8.05 (m, 4H), 8.14 (s, 1H), 8.97 (d, 1H); LC/MS (*m/z*): 500 (M+1)<sup>+</sup>.

#### Example 220

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3-Biphenyl-4-yl-(2S)-[(4'-*tert*-butyl-4-chloro-biphenyl-3-carbonyl)-amino]-propionic acid

(2S)-Amino-3-biphenyl-4-yl-propionic acid methyl ester (1.0g mg, 4.1 mmol) was reacted with 5-bromo-2-chloro-benzoic acid (1.07g mg, 5.3 mmol) as described in general procedure A yielding 3-biphenyl-4-yl-(2S)-(5-bromo-2-chloro-benzoyl-amino)-propionic acid (1.5g, 85%) as white solid.

35

3-Biphenyl-4-yl-(2S)-[(2-chloro-5-bromo-benzoyl-amino)-propionic acid (100mg, 0.23 mmol) was reacted with 4-trifluoromethyl-phenyl boronic acid (0.141 mg, 0.69 mmol) by following general procedure D yielding the title compound (114 mg, 75%) as a white solid.

<sup>1</sup>H-NMR(400 MHz, DMSO-*d*<sub>6</sub>): 2.98-3.02 (m, 1H), 3.24-3.28 (m, 1H), 4.71-4.73 (m, 1H), 7.25 (d, 1H), 7.31-7.34 (m, 1H), 7.38-7.41 (m, 4H), 7.56-7.60 (m, 5H), 7.70 (d, 2H), 7.74-7.77 (m, 3H), 8.9 (d, 1H); LC/MS (*m/z*): 524 (M+1)<sup>+</sup>.

5      Example 221

(2S)-[(4-Chloro-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid

10      (2S)-Amino-3-(4-bromo-phenyl)-propionic acid methyl ester (1.0g mg, 3.8 mmol) was reacted with 5-bromo-2-chloro-benzoic acid (1.09g mg, 4.5 mmol) as described in general procedure A yielding (2S)-(5-bromo-2-chloro-benzoyl-amino)-3-(4-bromo-phenyl)-propionic acid (1.35g, 75%).

15      (2S)-(5-Bromo-2-chloro-benzoyl-amino)-3-(4-bromo-phenyl)-propionic acid (100mg, 0.21 mmol) was reacted with 4-trifluoromethyl-phenyl-boronic acid (243 mg, 1.2 mmol) by following general procedure D yielding the title compound (114 mg, 75%) as a light yellow solid.

<sup>1</sup>H-NMR(400 MHz, DMSO-*d*<sub>6</sub>): 3.01-3.04 (m, 1H), 3.27-3.29 (m, 1H), 4.74-4.76 (m, 1H), 7.17 (d, 1H), 7.46 (d, 2H), 7.57 (d, 1H), 7.64 (d, 2H, J = 8 Hz), 7.67-7.82 (m, 9H), 8.91 (d, 1H, J = 8.4 Hz); LC/MS (*m/z*): 592 (M+1)<sup>+</sup>.

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Example 222

(2S)-[(4'-Methoxy-biphenyl-3-carbonyl)-amino]-3-(4'-methoxyl-biphenyl-4-yl)-propionic acid

25      (2S)-Amino-3-(4-bromo-phenyl)-propionic acid methyl ester (1.0g, 3.8 mmol) was reacted with 3-bromo-benzoic acid (0.91g, 4.5 mmol) as described in general procedure A yielding (2S)-(3-bromo-benzoyl-amino)-3-(4-bromo-phenyl)-propionic acid methyl ester (1.38g, 81%).

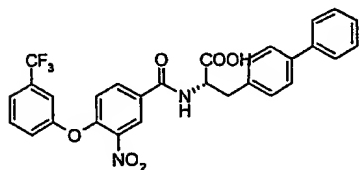
30      (2S)-(3-Bromo-benzoyl-amino)-3-(4-bromo-phenyl)-propionic acid methyl ester (100mg, 0.22 mmol) was reacted with 4-methoxy-phenyl-boronic acid (204 mg, 1.4 mmol) according to general procedure D yielding the title compound (90 mg, 83%) as a white solid.

<sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>): 3.08 (m, 1H), 3.22 (m, 1H), 3.74 (s, 3H), 3.76 (s, 3H), 4.38 (m, 1H), 6.96-7.01 (m, 3H), 7.25 (d, 2H), 7.43-7.48 (m, 3H), 7.52 (d, 2H), 7.62-7.07 (m, 3H), 7.70 (d, 1H), 7.87 (s, 1H), 8.10 (d, 1H); LC/MS (*m/z*): 482 (M+1)<sup>+</sup>.

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Example 223

## 3-Biphenyl-4-yl-(2S)-[3-nitro-4-(3-trifluoromethyl-phenoxy)-benzoylamino]-propionic acid

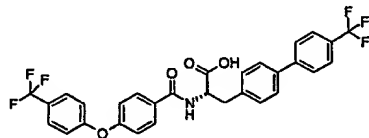


3-Nitro-4-(3-trifluoromethyl-phenoxy)-benzoic acid (530 mg, 81%) was prepared from 4-fluoro-3-nitro-benzoic acid (370 mg, 2.0 mmol) and 3-trifluoromethyl phenol (324 mg, 2.0 mmol) as in general procedure B. To Wang resin (60mg, 0.06 mmol, 1.1 mmol/g) loaded with 4-L-biphenylalanine were added 82 mg of (0.25 mmol) 3-nitro-4-(3-trifluoromethyl-phenoxy)-benzoic acid (82 mg, 0.25 mmol), 1.0 M DIC (1.5 mL, 1.5 mmol) in DMF, 1.0 M HOBt (1.5 mL, 1.5 mmol) in DMF, and a catalytic amount of DMAP. The resulting mixture was left on shaker overnight. The resin was washed with DMF, MeOH, DCM three times of each and cleaved with 20% TFA in DCM. The residue obtained after removing the solvent was purified by chromatography to give the title compound (26 mg, 79%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 3.35, 3.40 (ABX, 2H), 5.18 (dd, 1H), 6.64 (d, 1H), 7.03 (dd, 2H), 7.28 (m, 1H), 7.34 (m, 2H), 7.42 (m, 2H), 7.55 (m, 5H), 7.91 (dd, 1H), 8.21 (dd, 1H), 8.36 (d, 1H), 8.69 (d, 1H); LC/MS (*m/z*): 551 (M+1)<sup>+</sup>.

## Example 224

## 3-(4'-Trifluoromethyl-biphenyl-4-yl)-(2S)-[4-(4-trifluoromethyl-phenoxy)-benzoylamino]-propionic acid



4-(4-Trifluoromethyl-phenoxy)benzoic acid (474 mg, 80%) was prepared from 1-fluoro-4-trifluoromethyl benzene (328 mg, 2.0 mmol) and 4-hydroxy benzoic acid methyl ester (304 mg, 2.0 mmol) following general procedure B, then hydrolyzed following general procedure C to give the corresponding acid (450 mg, 80%). 3-(4'-Trifluoromethyl-biphenyl-4-yl)-(2S)-[4-(4-trifluoromethyl-phenoxy)-benzoylamino]-propionic acid methyl ester (121 mg, 82%) was prepared starting from the above acid (70mg, 0.25 mmol) and 2-amino-3-(4'-trifluoromethyl-biphenyl-4-yl)-(2S)-propionic acid methyl ester (108 mg, 0.30 mmol) according to general procedure A. The ester was hydrolyzed following general procedure C to give the title compound (105 mg, 89%)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 3.40 (m, 2H), 5.10 (m, 1H), 6.58 (m, 1H), 7.08 (m, 4H), 7.33 (m, 2H), 7.64 (m, 10H); LC/MS (*m/z*): 574 (M+1)<sup>+</sup>.

#### Example 225

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3-Biphenyl-4-yl-(2S)-[4-(5-trifluoromethyl-pyridin-2-yloxy)-benzoylamino]-propionic acid

5-(Trifluoromethyl)-2-pyridinol (1.63 g, 10 mmol) was reacted with 4-fluorobenzaldehyde (1.24 g, 10 mmol) as described in general procedure B. The resulting compound was oxidized by AgNO<sub>3</sub> (20 mmol) in 2N NaOH aq. solution (20 mL, 40 mmol) to afford 4-(5-(trifluoromethyl-pyridin-2-yloxy)-benzoic acid (5.10 g, 80%) as a white solid.

2-L-amino-3-biphenyl-4-yl-propionic acid methyl ester (128 mg, 0.5 mmol) was reacted with above 4-(5-(trifluoromethyl-pyridin-2-yloxy)-benzoic acid (142 mg, 0.5 mmol) as described in general procedure A. The resulting compound was hydrolyzed according to general procedure C to afford the title product (225 mg, 80%) as a white solid. <sup>1</sup>H-NMR(400 MHz, CDCl<sub>3</sub>): 3.21 (dd, 1H), 3.36 (dd, 1H), 5.02 (dd, 1H), 6.74(d, 1H), 7.39-7.27 (m, 8H), 7.56-7.48 (m, 5H), 7.67 (s, 1H), 7.79 (d, 2H); LC/MS (*m/z*): 507(M+1)<sup>+</sup>.

#### Example 226

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3-[4-(4-Trifluoromethyl-phenoxy)-phenyl]-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid

3-(4-Hydroxy-phenyl)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester (664 mg, 75%) was prepared starting from 4'-trifluoromethyl-biphenyl-4-carboxylic acid (532 mg, 2.0 mmol) and tyrosine methyl ester (462 mg, 2.0 mmol) according to general procedure A. The above compound (443 mg, 1.0 mmol) was treated with 1-fluoro-4-trifluorobenzene (246 mg, 1.5 mmol) following general procedure B to give 3-[4-(4-trifluoromethyl-phenoxy)-phenyl]-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester (305 mg, 52%). The ester was hydrolyzed following general procedure C to give the title compound (296 mg, 99%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 3.22, 3.36 (ABX, 2H), 5.04 (dd, 1H), 6.56 (d, 1H), 6.94 (m, 4H), 7.17 (m, 2H), 7.49 (d, 2H), 7.63 (m, 6H), 7.76 (d, 2H); LC/MS (*m/z*): 574 (M+1)<sup>+</sup>.

#### Example 227

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3-[4-(4-Cyano-phenoxy)-phenyl]-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid



3-(4-Hydroxy-phenyl)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester (664 mg, 75%) was prepared starting from 4'-trifluoromethyl-biphenyl-4-carboxylic acid (532 mg, 2.0 mmol) and tyrosine methyl ester (462 mg, 2.0 mmol) according to general procedure A. The above compound (443 mg, 1.0 mmol) was treated with 1-fluoro-4-cyanobenzene (181 mg, 1.5 mmol) following general procedure B to give 3-[4-(4-cyano-phenoxy)-phenyl]-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester (360 mg, 66%). The ester was hydrolyzed following general procedure C to give the title compound (345 mg, 99%)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 3.28, 3.44 (ABX, 2H), 5.12 (dd, 1H), 6.65 (d, 1H), 6.99 (m, 4H), 7.28 (m, 2H), 7.58 (d, 2H), 7.69 (m, 6H), 7.84 (d, 2H); LC/MS (*m/z*): 530 (M+1)<sup>+</sup>.

#### Example 228

(

2S)-(4-Benzoyloxy-benzoylamino)-3-biphenyl-4-yl-propionic acid

2-L-amino-3-biphenyl-4-yl-propionic acid methyl ester (255 mg, 1.0 mmol) was reacted with 4-(benzyloxy)-benzoic acid (228 mg, 1.0 mmol) as described in general procedure A. The resulting compound was hydrolyzed according to general procedure C to afford the title product (370mg, 82%) as a white solid. <sup>1</sup>H-NMR(400 MHz, CDCl<sub>3</sub>): 3.31 (dd, 1H), 3.40 (dd, 1H), 5.09-5.05 (m, 3H), 6.56 (d, 1H), 6.96 (d, 2H), 7.27 (d, 2H), 7.36-7.32 (m, 2H), 7.43-7.38 (m, 6H), 7.57-7.52 (m, 4H), 7.67 (d, 2H); LC/MS (*m/z*): 452(M+1)<sup>+</sup>.

By analogous methods to those described above the following compounds were synthesized

EXAMPLE	NAME	LC/MS ( <i>m/z</i> )
229	3-Biphenyl-4-yl-(2S)-[(4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid	490
230	3-Biphenyl-4-yl-(2S)-[(3-chloro-4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid	524
231	3-Biphenyl-4-yl-(2S)-[4-(4-nitro-phenoxy)-benzoylamino]-propionic acid	483

EXAMPLE	NAME	LC/MS (m/z)
232	3-Biphenyl-4-yl-(2S)-[4-(3,4-dimethyl-phenoxy)-3-nitro-benzoylamino]-propionic acid	511
233	3-Biphenyl-4-yl-(2S)-[(3'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid	490
234	3-Biphenyl-4-yl-(2S)-[(3',5'-bis-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid	558
235	3-Biphenyl-4-yl-(2S)-[(4'-tert-butyl-biphenyl-4-carbonyl)-amino]-propionic acid	478
236	3-Biphenyl-4-yl-(2S)-[(4'-dimethylamino-biphenyl-4-carbonyl)-amino]-propionic acid	465
237	3-Biphenyl-4-yl-(2S)-[(4'-methoxy-biphenyl-4-carbonyl)-amino]-propionic acid	452
238	3-Biphenyl-4-yl-2-[(3',4'-dichloro-biphenyl-4-carbonyl)-amino]-propionic acid	490
239	3-Biphenyl-4-yl-(2S)-[(5'-chloro-2'-methoxy-biphenyl-4-carbonyl)-amino]-propionic acid	486
240	(2S)-[(3'-Amino-biphenyl-4-carbonyl)-amino]-3-biphenyl-4-yl-propionic acid	437
241	(2S)-[(4'-Trifluoromethoxy-biphenyl-4-carbonyl)-amino]-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid	574
242	3-(4'-Trifluoromethoxy-biphenyl-4-yl)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid	574
243	3-(4-Pyridin-4-yl-phenyl)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid	491
244	3-Biphenyl-4-yl-(2S)-[4-(5-trifluoromethyl-pyridin-2-yl)-benzoylamino]-propionic acid	491
245	3-(4-Pyridin-4-yl-phenyl)-(2S)-[4-(5-trifluoromethyl-pyridin-2-yl)-benzoylamino]-propionic acid	492

EXAMPLE	NAME	LC/MS (m/z)
246	3-(4'-Methanesulfonylamino-biphenyl-4-yl)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid	583
247	3-(3'-Chloro-4'-fluoro-biphenyl-4-yl)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid	542
248	3-(4'-Cyano-biphenyl-4-yl)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid	515
249	3-(5-Phenyl-pyridin-2-yl)-2-[(4'-trifluoromethoxy-biphenyl-4-carbonyl)-amino]-propionic acid	507
250	3-(4'-Amino-biphenyl-4-yl)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid	505
251	3-(4'-Dimethylamino-biphenyl-4-yl)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid	533
252	3-(4'-Trifluoromethoxy-biphenyl-4-yl)-(2S)-[4-(5-trifluoromethyl-pyridin-2-yl)-benzoylamino]-propionic acid	575
253	3-(4'-Trifluoromethyl-biphenyl-4-yl)-(2S)-[4-(5-trifluoromethyl-pyridin-2-yl)-benzoylamino]-propionic acid	559
254	3-(4'-Trifluoromethoxy-biphenyl-4-yl)-(2S)-[4-(4-trifluoromethyl-phenoxy)-benzoylamino]-propionic acid	590
255	3-Biphenyl-4-yl-(2S)-[4-(4-trifluoromethyl-phenoxy)-benzoylamino]-propionic acid	506
256	3-Biphenyl-4-yl-(2S)-[4-(4-formyl-phenoxy)-benzoylamino]-propionic acid	466

EXAMPLE	NAME	LC/MS (m/z)
257	3-(5'-Chloro-2'-methoxy-biphenyl-4-yl)-(2S)- [(4'-trifluoromethyl-biphenyl-4-carbonyl)- amino]-propionic acid	554
258	3-(4'-Chloro-biphenyl-4-yl)-(2S)-[(4'- trifluoromethyl-biphenyl-4-carbonyl)-amino]- propionic acid	524
259	3-Biphenyl-4-yl-(2R)-[(4'-trifluoromethyl- biphenyl-4-carbonyl)-amino]-propionic acid	490
260	3-(5-Phenyl-pyridin-2-yl)-2-[(4'-trifluoromethyl- biphenyl-4-carbonyl)-amino]-propionic acid	491
261	3-(3'-Acetylamino-biphenyl-4-yl)-(2S)-[(4'- trifluoromethyl-biphenyl-4-carbonyl)-amino]- propionic acid	547
262	3-(3',4'-Dichloro-biphenyl-4-yl)-(2S)-[(4'- trifluoromethyl-biphenyl-4-carbonyl)-amino]- propionic acid	558
263	3-(5'-Fluoro-2'-methoxy-biphenyl-4-yl)-(2S)- [(4'-trifluoromethyl-biphenyl-4-carbonyl)- amino]-propionic acid	538
264	3-[4'-(Acetylamino-methyl)-biphenyl-4-yl]- (2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)- amino]-propionic acid	561
265	3-(4'-Trifluoromethoxy-biphenyl-4-yl)-(2S)-[4- (5-trifluoromethyl-pyridin- 2-yloxy)-benzoylamino]-propionic acid	591
266	3-Biphenyl-4-yl-(2S)-[4-(5-trifluoromethyl- pyridin-2-yloxy)-benzoylamino]-propionic acid	507
267	3-[4-(4-Nitro-phenoxy)-phenyl]-(2S)-[(4'- trifluoromethyl-biphenyl-4-carbonyl)-amino]- propionic acid	553
268	3-[4-(4-Formyl-phenoxy)-phenyl]-(2S)-[(4'- trifluoromethyl-biphenyl-4-carbonyl)-amino]- propionic acid	534

EXAMPLE	NAME	LC/MS (m/z)
269	3-(4-Thiophen-3-yl-phenyl)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid	496
270	3-(4-Thiophen-3-yl-phenyl)-(2S)-[(4'-trifluoromethoxy-biphenyl-4-carbonyl)-amino]-propionic acid	512
271	(2S)-(4-Benzoyloxy-benzoylamino)-3-(4'-trifluoromethoxy-biphenyl-4-yl)-propionic acid	536
272	3-(2'-Phenoxy-biphenyl-4-yl)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid	537
273	3-(4'-Phenoxy-biphenyl-4-yl)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid	582

## Example 274

- 5 3-Biphenyl-4-yl-(2S)-[2-(4-*tert*-butyl-benzoylamino)-5-iodo-benzoyl-amino]-propionic acid (2S)-(2-Amino-5-iodo-benzoyl-amino)-3-biphenyl-4-yl-propionic acid methyl ester (1.53g, 80%) was prepared from (2S)-amino-3-biphenyl-4-yl-propionic acid methyl ester (1.0g, 4.1 mmol), 5-iodo-2-amino-benzoic acid (1.23g, 4.9 mmol) as described in general procedure A .
- 10 3-Biphenyl-4-yl-(2S)-[2-(4-*tert*-butyl-benzoylamino)-5-iodo-benzoyl-amino]-propionic acid methyl ester was prepared as a white solid from (2S)-(2-amino-5-iodo-benzoyl-amino)-3-biphenyl-4-yl-propionic acid methyl ester (1.0g, 2 mmol) prepared above, pyridine (1.58 g, 4 mmol ), *t*-butyl-benzoyl chloride (1.20 g, 2.5 mmol) as described in general procedure K. The title compound (1.23 g, 100%) as a white solid ((1.23 g, 100%) was obtained after
- 15 hydrolysis according to general procedure C
- <sup>1</sup>H-NMR(400 MHz, DMSO-*d*<sub>6</sub>): 1.26 (s, 9H), 3.09-3.19 (m, 1H), 3.21-3.29 (m, 1H), 4.74-4.76 (m, 1H), 7.27-7.29 (m, 1H ), 7.42-7.39 (m, 4H), 7.44-7.57 (m, 7H), 7.67-7.77 (m, 3H), 7.99 (s, 1H), 8.54 (d, 1H), 9.32 (d, 1H), 11.98 (s, 1H); LC/MS (*m/z*): 647 (M+1)<sup>+</sup>.

## 20 Example 275

3-Biphenyl-4-yl-(2S)-{[4-(4-*tert*-butyl-benzoylamino)-3'-trifluoromethyl-biphenyl-3-carbonyl]-amino}-propionic acid

Example 274

5

(100 mg, 0.15 mmol) was reacted with 3-trifluoromethyl phenyl boronic acid (87.5 mg, 4.5 mmol) as described in general procedure D yielding the title compound (92 mg, 90%) as white solid. LC/MS (*m/z*): 665 (M+1)<sup>+</sup>.

10

Example 276

3-Biphenyl-4-yl-(2S)-{[4-(4-*tert*-butyl-benzoylamino)-4'-nitro-biphenyl-3-carbonyl]-amino}-propionic acid

15

Example 274 (100 mg, 0.15 mmol) was reacted with 4-nitro-phenyl boronic acid (77 mg, 4.5 mmol) as described in general procedure D yielding the title compound (92 mg, 90%) as white solid. LC/MS (*m/z*): 642 (M+1)<sup>+</sup>.

Example 277

20

3-Biphenyl-4-yl-(2S)-{[4-(4-*tert*-butyl-benzoylamino)-3'-chloro-4'-fluoro-biphenyl-3-carbonyl]-amino}-propionic acid

Example 274

25

(100 mg, 0.15 mmol) was reacted with 3-chloro-4-fluoro-phenyl boronic acid (80 mg, 4.5 mmol) as described in general procedure D yielding the title compound (95 mg, 95%) as a white solid.

30

<sup>1</sup>H-NMR(400 MHz, DMSO-*d*<sub>6</sub>): 1.28 (s, 9H), 3.09-3.19 (m, 1H), 3.21-3.29 (m, 1H), 4.74-4.76 (m, 1H), 7.27-7.29 (m, 1H), 7.32-7.44 (m, 6H), 7.44-7.57 (m, 7H), 7.50-7.59 (m, 2H), 7.71-7.77 (m, 2H), 7.80-7.86 (m, 2H), 7.88-7.90 (m, 3H), 8.3 (s, 2H), 8.7 (d, 1H), 9.38 (d, 1H), 12.00 (s, 1H); LC/MS (*m/z*): 647 (M+1)<sup>+</sup>.

Example 278

35

3-Biphenyl-4-yl-(2S)-[4-(4-*tert*-butyl-benzoylamino)-5-(4-chloro-3-trifluoromethyl-phenoxy)-benzoylamino]-propionic acid

Example 274 (100 mg, 0.15 mmol), 4-chloro-3-trifluoromethyl phenol (60.4 mg, 0.3 mmol), cesium carbonate (0.3 mmol), CuI (0.15 mmol) were added to 10 mL of toluene containing 4Å molecular sieves. The mixture was degassed and filled with nitrogen three times. This mixture was then heated to reflux under nitrogen and followed by HPLC until completion of the reaction. The reaction with diluted with toluene and filtered. The toluene was evaporated, and the residue was dissolved in ethyl acetate washed with 2M HCl and then saturated NaCl. The title compound (70 mg, 65% ) was isolated by flash chromatography (silica, 1 % MeOH in DCM) as a white solid. <sup>1</sup>H-NMR(400 MHz, CDCl<sub>3</sub>): 1.35 (s, 9H), 3.22-3.27 (m, 1H), 3.32-3.37 (m, 1H), 5.03-5.13 (m, 1H), 6.69 (d, 1H), 6.98-7.01 (m, 1H), 7.13-7.18 (m, 4H), 7.28-7.53 (m, 10H), 7.93 (d, 1H), 8.85 (d, 1H), 11.72 (s, 1H); LC/MS (*m/z*): 715 (M+1)<sup>+</sup>.

#### Example 279

3-Biphenyl-4-yl-(2S)-[2-(3,5-bis-trifluoromethyl-benzoylamino)-5-bromo-benzoylamino]-propionic acid

To a solution of fmoc-L-biphenylalanine (40.0 mmol) in DMF (40 mL) was added Wang resin (16.0 mmol), HOBt (40.0 mmol) in DMF (40mL), DIC (40.0 mmol) in DMF (40mL) and DMAP (0.40 mmol) and the mixture was shaken overnight. The reaction mixture was drained and the resin washed with DMF, methanol and DCM (3x 150mL each solvent).

The resulting resin-bound fmoc-L-biphenylalanine was deprotected with 20% piperidine in DMF (150mL) for 2 hours. The reaction mixture was drained and washed with DMF, methanol and DCM (3x 150mL each solvent).

To the resin-bound L-biphenylalanine (12 mmol), a solution of 2-amino-5-bromobenzoic acid (30 mmol) in DMF (30mL), HOBt (30 mmol) in DMF (30mL) and DIC (30 mmol) in DMF (30mL) were added and the mixture was shaken overnight. The reaction mixture was drained and washed with DMF, methanol and DCM (3x 150mL each solvent).

To the resin-bound (S)-2-(2-amino-5-bromo-benzoylamino)-3-biphenyl-4-yl-propionic acid (0.12mmol) was added a solution of 3,5-bis-(trifluoromethyl)benzoyl chloride (0.3mmol) and pyridine (0.3 mmol) and the mixture agitated for 72 hours. The reaction mixture was drained and washed with DMF, methanol and DCM (3x 5mL each solvent).

Resin bound (S)-3-biphenyl-4-yl-2-[2-(3,5-bistrifluoromethyl-benzoylamino)-5-bromo-benzoylamino] propionic acid was treated with 20% TFA in DCM (2mL) for 1 hour. The filtrate was collected and evaporated to give (S)-3-biphenyl-4-yl-2-[2-(3,5-bis(trifluoromethyl)-benzoylamino)-5-bromo-benzoylamino] propionic acid (0.0412 g, 50%). The product was purified via chromatography (silica, DCM/ethyl acetate). LC/MS (*m/z*): 680 (M+1)<sup>+</sup>.

## Example 280

(2S)-[5-Bromo-(2S)-(2-cyclopentyl-acetylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

- 5 (S)-(2-Amino-5-bromo-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester (1.53g, 80%) was prepared from (2S)-Amino-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester HCl salt (1.0g, 2.6 mmol, 5-bromo-2-amino-benzoic acid (0.5g, 2.9 mmol) as described in general procedure A .
- 10 (S)-(2-Amino-5-bromo-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester (0.2g, 0.04 mmol) in 5 ml of DCM was reacted with cyclopentyl acetyl chloride (82.6 mg, 0.06 mmol) and pyridine (60mg, 0.08 mmol) as described in general procedure K. The resulting ester was hydrolyzed according to the general procedure C to afford the title compound (0.2g, 83.3%) as a white solid. LCMS: 642 (M+1)<sup>+</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>): 1.1-1.26 [m, 3H], 1.5-1.75 [m, 3 H], 1.8-1.90 [m, 2 H], 2.2-2.41 [m, 2H], 2.48 [d, 1H], 3.1-3.4 [m, 2H], 5.0-5.1 [m, 1H], 6.6 [d, 1H], 6.89-6.97 [m, 4H], 7.18-7.26 [m, 6H], 7.43-7.52 [m, 5H], 8.48 (d, 1), 10.73 (s, 1H).
- 15

## EXAMPLE 281

- 20 (2S)-[5-Bromo-2-(3,3,5-trimethyl-hexanoylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid
- A solution of (2S)-(2-amino-5-bromo-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester (54.5 mg, 0.10 mmol) from example 294 in 1 mL dry CH<sub>2</sub>Cl<sub>2</sub> was treated with 3,3,5-trimethylhexanoyl chloride (1.2 eq., 23 microL, 0.12 mmol) and pyridine
- 25 (1.5 eq., 12 microL, 0.15 mmol) in succession and stirred under an atmosphere of dry N<sub>2</sub> for one hour, then concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes, EtOAc) to afford the desired amide, (2S)-[5-Bromo-2-(3,3,5-trimethyl-hexanoylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester, in quantitative yield (68 mg, 100%). The methyl ester (20 mg, 29 micromol) was
- 30 dissolved in 2.0 mL THF and 0.5 mL MeOH and saponified with 2N aqueous LiOH solution (0.25 mL), as described in general procedure C, to afford the title compound, (2S)-[5-Bromo-2-(3,3,5-trimethyl-hexanoylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid (20 mg, 100%), as a white solid. LCMS 673 (M+1)<sup>+</sup>. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) 10.74 [s, 1H], 8.51 [d, 1H], 7.51 [m, 3H], 7.43 [m, 2H], 7.27 - 7.30 [m, 2H], 7.16 - 7.26 [m, 5H], 6.98 [d, 2H], 6.88 [d, 2H], 6.59 [d, 1H], 5.03 [dd, 1H], 3.28 [dq, 2H], 2.36 [m, 1H], 2.14 [m, 1H], 1.11-1.25 [m, 3H], 1.00 [s, 3H], 0.92 [s, 3H], 0.91 [d, 6H].
- 35



## EXAMPLE 282

(  
2S)-[5-Chloro-2-(4-phenoxy-benzoylamino)-benzoylamino]-3-(2'-isopropoxy-biphenyl-4-yl)-propionic acid

5           2-Amino-5-chloro-benzoic acid (0.702g, 4.09mmol) was coupled with 2-Amino-3- (4-bromo-phenyl)-propionic acid methyl ester hydrochloride (1 g, 4.09mmol) using HBTU (1.86 g, 4.908mmol) and diisopropylethylamine (1.32 ml, 10.22mmol) as per general procedure A to yield the 2-(2-amino-5-chloro-benzoylamino)-3-(4-bromo-phenyl)-propionic acid methyl ester in 60% yield.

10           The above compound (0.500g, 1.21mmol) was reacted with 4-phenoxy-benzoyl chloride (0.337g, 1.45mmol) in dry dichloromethane at 0°C as described in general procedure J to get 3-(4-Bromo-phenyl)-2-[5-chloro-2- (4-phenoxy-benzoylamino)-benzoylamino]-propionic acid methyl ester (0.590g, 80%).

15           The above compound (0.100g, 0.164mmol) was then subjected to Suzuki coupling with 2-isopropoxyphenylboronic acid (0.059g, 0.328mmol) and with Pd (PPh<sub>3</sub>) (0.0189g, .016mmol) and 2N Na<sub>2</sub>CO<sub>3</sub> (0.410ml, 0.410mmol) as per general procedure D to yield (2S)-[5-chloro-2- (4-phenoxy-benzoylamino)-benzoylamino]-3-(2'-isopropoxy-biphenyl-4-yl)-propionic acid methyl ester which was further hydrolyzed as per general procedure C to give the title compound (0.050g, 50%)%. <sup>1</sup>H-NMR(400 MHz, CDCl<sub>3</sub>): 1.56(d, 6H), 3.65(dddd, 2H), 4.76(m, 1H), 5.42( m, 1H), 7.30-7.38( m, 6H), 7.39-7.58(m, 8H), 7.59-7.83(m, 6H), 8.27  
20 (m, 2H), 9.01(d, 1H). LC/MS (m/z): 649(M+1).

By analogous methods to those described above the following compounds were synthesized.

EXAMPLE	NAME	LC/MS (m/z)
283	3-Biphenyl-4-yl-(2S)-[2-(4-tert-butyl-benzoylamino)-benzoylamino]-propionic acid	521
284	3-Biphenyl-4-yl-(2S)-[5-chloro-2-(2,4-dichloro-benzoylamino)-benzoylamino]-propionic acid	567
285	(2S)-({4-[(Biphenyl-4-carbonyl)-amino]-3'-chloro-4'-fluoro-biphenyl-3-carbonyl}-amino)-3-biphenyl-4-yl-propionic acid	669
286	(2S)-{2-[(Biphenyl-4-carbonyl)-amino]-benzoylamino}-3-(3'-chloro-4'-fluoro-biphenyl-4-yl)-propionic acid	593
287	(2S)-[2-(4-tert-Butyl-benzoylamino)-benzoylamino]-3-(3'-chloro-4'-fluoro-biphenyl-4-yl)-propionic acid	573
288	3-Biphenyl-4-yl-(2S)-[5-bromo-2-(4-tert-butyl-benzoylamino)-benzoylamino]-propionic acid	600
289	3-Biphenyl-4-yl-(2S)-{[4-(4-tert-butyl-benzoylamino)-4'-cyano-biphenyl-3-carbonyl]-amino}-propionic acid	622
290	(2S)-{[4'-Amino-4-(4-tert-butyl-benzoylamino)-biphenyl-3-carbonyl]-amino}-3-biphenyl-4-yl-propionic acid	612
291	3-Biphenyl-4-yl-(2S)-{[4-(4-tert-butyl-benzoylamino)-3'-cyano-biphenyl-3-carbonyl]-amino}-propionic acid	622
292	(2S)-({3-[(Biphenyl-4-carbonyl)-amino]-naphthalene-2-carbonyl}-amino)-3-(3'-chloro-4'-fluoro-biphenyl-4-yl)-propionic acid	643
293	(2S)-{[3-(4-tert-Butyl-benzoylamino)-naphthalene-2-carbonyl]-amino}-3-(3'-chloro-4'-fluoro-biphenyl-4-yl)-propionic acid	623

EXAMPLE	NAME	LC/MS (m/z)
294	(2S)-{[3'-Aminomethyl-4-(4-tert-butyl-benzoylamino)-biphenyl-3-carbonyl]-amino}-3-biphenyl-4-yl-propionic acid	626
295	3-Biphenyl-4-yl-(2S)-{[4-(4-tert-butyl-benzoylamino)-4'-carbamidoyl-biphenyl-3-carbonyl]-amino}-propionic acid	639
296	3-Biphenyl-4-yl-(2S)-[2-(4-tert-butyl-benzoylamino)-5-(4-nitro-phenoxy)-benzoylamino]-propionic acid	658
297	(2S)-{[4-(4-tert-Butyl-benzoylamino)-3'-trifluoromethyl-biphenyl-3-carbonyl]-amino}-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionic acid	733
298	(2S)-{[4-(4-tert-Butyl-benzoylamino)-3'-chloro-4'-fluoro-biphenyl-3-carbonyl]-amino}-3-(3'-chloro-4'-fluoro-biphenyl-4-yl)-propionic acid	701
299	(2S)-{[4-(4-tert-Butyl-benzoylamino)-4'-trifluoromethyl-biphenyl-3-carbonyl]-amino}-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid	733
300	3-Biphenyl-4-yl-(2S)-[5-bromo-2-(3-phenyl-acryloylamino)-benzoylamino]-propionic acid	570
301	3-Biphenyl-4-yl-(2S)-[5-bromo-2-[(naphthalene-2-carbonyl)-amino]-benzoylamino]-propionic acid	594
302	3-Biphenyl-4-yl-(2S)-[5-bromo-2-(2-cyclopentyl-acetylamino)-benzoylamino]-propionic acid	550
303	3-Biphenyl-4-yl-(2S)-[5-bromo-2-(4-trifluoromethoxy-benzoylamino)-benzoylamino]-propionic acid	628
304	3-Biphenyl-4-yl-(2S)-[5-bromo-2-(4-phenoxy-butyrylamino)-benzoylamino]-propionic acid	602
305	3-Biphenyl-4-yl-(2S)-[5-bromo-2-[2-(4-tert-butyl-phenoxy)-acetylamino]-benzoylamino]-propionic acid	630

EXAMPLE	NAME	LC/MS (m/z)
306	(2S)-[2-(4-tert-Butyl-benzoylamino)-5-chloro-benzoylamino]-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid	647
307	2-[5-Bromo-(2S)-(4-tert-butyl-benzoylamino)-benzoylamino]-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid	692
308	3-Biphenyl-4-yl-(2S)-[4-chloro-2-(4-trifluoromethyl-benzoylamino)-benzoylamino]-propionic acid	567
309	3-Biphenyl-4-yl-(2S)-[2-(4-tert-butyl-benzoylamino)-5-(4-trifluoromethyl-phenoxy)-benzoylamino]-propionic acid	681
310	3-Biphenyl-4-yl-(2S)-[2-(4-trifluoromethyl-benzoylamino)-5-(4-trifluoromethyl-phenoxy)-benzoylamino]-propionic acid	693
311	3-Biphenyl-4-yl-(2S)-[2-(4-tert-butyl-benzoylamino)-4-(4-trifluoromethyl-phenoxy)-benzoylamino]-propionic acid	681
312	(2S)-[2-(4-tert-Butyl-benzoylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	647
313	(2S)-[5-Chloro-2-(4-phenoxy-benzoylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	683
314	(2S)-[2-(4-Benzoyloxy-benzoylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	697
315	(2S)-(5-Bromo-2-phenylacetyl-amino-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	650
316	(2S)-[5-Bromo-2-(4-bromo-benzoylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	715

EXAMPLE	NAME	LC/MS (m/z)
317	(2S)-{5-Bromo-2-[2-(4-fluoro-phenyl)-acetyl-amino]-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	668
318	2-[5-Bromo-(2S)-[(naphthalene-2-carbonyl)-amino]-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	686
319	(2S)-{5-Bromo-2-[(naphthalene-1-carbonyl)-amino]-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	686
320	(2S)-[5-Chloro-2-(3-phenoxy-benzoylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	683
321	-S-[2-(3-Benzoyloxy-benzoylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	697
322	(2S)-[5-Bromo-2-(4-phenoxy-benzoylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	728
323	(2S)-[5-Bromo-2-(4-hexyl-benzoylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	720
324	(2S)-[5-Bromo-2-(4-fluoro-benzoylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	654
325	(2S)-{5-Bromo-2-[(thiophene-2-carbonyl)-amino]-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	642
326	(2S)-[5-Bromo-2-(2-thiophen-2-yl-acetyl-amino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	656
327	(2S)-[5-Bromo-2-(cyclopropanecarbonyl-amino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	600

EXAMPLE	NAME	LC/MS (m/z)
328	(2S)-[5-Bromo-2-(cyclobutanecarbonyl-amino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	614
329	(2S)-[5-Bromo-2-(cyclopentanecarbonyl-amino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	628
330	(2S)-[5-Bromo-2-(2-propyl-pentanoylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	658
345	(2S)-[5-Bromo-2-(2-phenoxy-propionylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	680
332	(2S)-[2-(3,5-Bis-trifluoromethyl-benzoylamino)-5-chloro-benzoylamino]-3-(3'-phenoxy-biphenyl-4-yl)-propionic acid	727
333	(2S)-[5-Bromo-2-(3,4,5-trimethoxy-benzoylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	726
334	(2S)-[2-[(Adamantane-1-carbonyl)-amino]-5-bromo-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	694
335	(2S)-[5-Bromo-2-[[1-(4-chloro-phenyl)-cyclopropanecarbonyl]-amino]-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	710
336	(2S)-[5-Bromo-2-[[1-(2,4-dichloro-phenyl)-cyclopropanecarbonyl]-amino]-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	744
337	(2S)-[5-Bromo-2-[(2,2-dichloro-1-methyl-cyclopropanecarbonyl)-amino]-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	682

EXAMPLE	NAME	LC/MS (m/z)
338	(2S)-{5-Chloro-2-[(6-chloro-pyridine-3-carbonyl)-amino]-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	626
339	(2S)-{5-Chloro-2-[[1-(4-trifluoromethyl-pyrimidin-2-yl)-piperidine-4-carbonyl]-amino]-enzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	744
340	(2S)-{5-Bromo-2-[(1-phenyl-cyclopropanecarbonyl)-amino]-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	676
341	(2S)-{5-Bromo-2-[(2-phenyl-cyclopropanecarbonyl)-amino]-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	676
342	(2S)-[5-Chloro-2-(2-phenoxy-benzoylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	683
343	3-(2'-Benzyloxy-biphenyl-4-yl)-(2S)-[2-(3,5-bis-trifluoromethyl-benzoylamino)-5-chloro-benzoylamino]-propionic acid	741
344	(2S)-{5-Chloro-2-[(6-phenoxy-pyridine-3-carbonyl)-amino]-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	684
345	(2S)-[5-Chloro-2-(4-phenoxy-benzoylamino)-benzoylamino]-3-(2'-cyclopentyloxy-biphenyl-4-yl)-propionic acid	675
346	(2S)-[5-Chloro-2-(4-phenoxy-benzoylamino)-benzoylamino]-3-[2'-(4-trifluoromethyl-benzyloxy)-biphenyl-4-yl]-propionic acid	765
347	3-[2'-(4-tert-Butyl-benzyloxy)-biphenyl-4-yl]-(2S)-[5-chloro-2-(4-phenoxy-benzoylamino)-benzoylamino]-propionic acid	753

EXAMPLE	NAME	LC/MS (m/z)
348	(2S)-[5-Chloro-2-(4-[1,2,3]thiadiazol-4-yl-benzoylamino)benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	675
349	(2S)-[5-Chloro-2-[4-(pyridin-4-ylmethoxy)-benzoylamino]benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	698
350	(2S)-(5-Chloro-2-[[1-(4-chloro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino]-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	759
351	(2S)-(5-Chloro-2-[[1-(4-chloro-phenyl)-5-propyl-1H-pyrazole-4-carbonyl]-amino]-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	733
352	(2S)-[5-Bromo-2-(3-phenyl-propionylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	664
353	(2S)-[2-(3,5-Bis-trifluoromethyl-benzoylamino)-5-chloro-benzoylamino]-3-[2'-(4-pentyl-phenoxy)-biphenyl-4-yl]-propionic acid	796
354	(2S)-{2-[(Benzofuran-2-carbonyl)-amino]-5-bromo-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	676
355	(2S)-{2-[(Benzo[b]thiophene-2-carbonyl)-amino]-5-bromo-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	692
356	(2S)-{5-Bromo-2-[(3-chloro-benzo[b]thiophene-2-carbonyl)-amino]-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	726

## Example 357

5 (2S)-{2-[(3,5-Bis-trifluoromethyl-benzoyl)-pentyl-amino]-5-chloro-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid



(2S)-amino-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester (192 mg, 0.5 mmol), which was prepared in the general section of syntheses of amino acids, was reacted with 5-bromoanthranilic acid (90 mg, 0.5 mmol) as described in general procedure A. The resulting crude compound was alkylated by valeraldehyde (86 mg, 1.0 mmol) as described in general reductive amination procedure E. The purified compound was reacted with 3,5-bis(trifluoromethyl)benzoyl chloride (210 mg, 0.75 mmol) as described in general procedure F. The resulting compound was hydrolyzed according to general procedure C to afford the title product (200 mg, 50%) as a white solid. <sup>1</sup>H-NMR(400 MHz, CDCl<sub>3</sub>): 0.86 (t, 3H), 3.71-2.91 (m, 8H), 4.29-4.23 (m, 1H), 4.85 (broad, 1H), 5.09-4.99 (m, 1H), 6.91-6.87 (m, 2H), 7.03-6.96 (m, 2H), 7.30-7.15 (m, 8H), 7.59-7.35 (m, 4H), 8.11-7.91 (m, 2H), 8.52 (s, 1H) LC/MS (*m/z*): 797(M+1)<sup>+</sup>.

#### Example 358

(2S)-{2-[(Biphenyl-4-carbonyl)-(4-methyl-benzyl)-amino]-5-chloro-benzoylamino}-3-biphenyl-4-yl-propionic acid

To the resin-bound L-biphenylalanine (1.2 mmol) which was made in example 279, a solution of 2-amino-5-chloro benzoic acid (3.0 mmol), HOBt (30 mmol), DIC (30 mmol) and DMAP (0.03 mmol) in DMF (30mL) were added and the mixture was shaken overnight. The reaction mixture was drained and washed with DMF, methanol and DCM (3x 150mL each solvent).

To the resin-bound (2S)-(2-amino-5-chloro-benzoylamino)-3-biphenyl-4-yl-propionic acid (0.12mmol) synthesized above was suspended in DCE (5 mL) was added 4-methyl benzaldehyde (0.6 mmol), acetic acid (0.6 mmol) and sodium cyanoborohydride (1.2 mmol) and the mixture was shaken overnight. Upon completion of the reaction, the reaction mixture was drained and washed with DMF, methanol and DCM (3x 5mL each solvent).

To the resin-bound 3-Biphenyl-4-yl-(2S)-[5-chloro-2-(4-methyl-benzylamino)-benzoylamino]-propionic acid (0.12mmol) was added a solution of Biphenyl-4-carbonyl chloride (0.3mmol) and pyridine (0.3 mmol) and the mixture agitated for 24 hours. The reaction mixture was drained and washed with DMF, methanol and DCM (3x 5mL each solvent).

Resin bound 2S-{2-[(Biphenyl-4-carbonyl)-(4-methyl-benzyl)-amino]-5-chloro-benzoylamino}-3-biphenyl-4-yl-propionic acid was treated with 20% TFA in DCM (2mL) for 1 hour. The filtrate was collected and evaporated to give 10 mg of the title compound with 95% purity. LC/MS (*m/z*): 679 (*m* + 1)<sup>+</sup>

By analogous methods to those described above the following Examples were synthesized.

EXAMPLE	NAME	LC/MS (m/z)
359	3-Biphenyl-4-yl-(2S){5-chloro-2-[(3,5-dichloro-benzoyl)-(4-methyl-benzyl)-amino]-benzoylamino}-propionic acid	671
360	(2S)-{2-[(Biphenyl-4-carbonyl)-(3-phenyl-propyl)-amino]-5-chloro-benzoylamino}-3-biphenyl-4-yl-propionic acid	693
361	3-Biphenyl-4-yl-(2S)-{5-chloro-2-[(2,4-dichloro-benzoyl)-(3-phenyl-propyl)-amino]-benzoylamino}-propionic acid	685
362	(2S)-{2-[(Biphenyl-4-carbonyl)-biphenyl-4-ylmethyl-amino]-5-chloro-benzoylamino}-3-biphenyl-4-yl-propionic acid	741
363	3-Biphenyl-4-yl-(2S)-{2-[biphenyl-4-ylmethyl-(2,4-dichloro-benzoyl)-amino]-5-chloro-benzoylamino}-propionic acid	733
364	(2S)-{2-[(Biphenyl-4-carbonyl)-(4-isopropyl-benzyl)-amino]-5-chloro-benzoylamino}-3-biphenyl-4-yl-propionic acid	707
365	(2S)-{2-[(Biphenyl-4-carbonyl)-(4-isopropoxy-benzyl)-amino]-5-chloro-benzoylamino}-3-biphenyl-4-yl-propionic acid	723
366	(2S)-{5-Bromo-2-[(2-methyl-butyl)-(4-phenoxy-benzoyl)-amino]-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	798

Example 367

5

(2S)-[5-Chloro-2-(5-dibutylamino-naphthalene-1-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester

A solution of 2-(2-amino-5-chloro-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid (0.05g, 0.1 mmol) [ prepared by reacting (2S)-amino-3-(2'-phenoxy-biphenyl-4-yl) propionic acid methyl ester hydrochloride salt and 2-amino-5-chlorobenzoic acid by general procedure A ] in CH<sub>2</sub>Cl<sub>2</sub> was treated with (0.035g, 0.1 mmol) of bansyl chloride according to the general  
 5 procedure F. Product was purified by flash column chromatography on silicagel using ethyl acetate hexanes to give product as pale yellow solid (0.06g, 74.0% yield).

<sup>1</sup>HNMR (400MHz, CDCl<sub>3</sub>) : 0.8 (t, 6H), 1.14-1.28 (m, 4H), 1.34-1.44 (m, 4H), 2.98-3.11 (m, 5H), 3.16 (dd, 1H), 3.73 (s, 3H), 4.91 (dd, 1H), 6.42 (d, 1H), 6.88 (d, 2H), 6.93-7.20 (m, 4H),  
 7.16-7.32 (m, 7H ), 7.40-7.47 (m, 4H), 7.54-7.61 (m, 2H), 8.24-8.29 (m, 1H), 8.35 (d, 1H),  
 10 8.56 (d, 1H), 11.11 (s, 1H).

LC/MS (*m/z*): 818.3 (M+1)<sup>+</sup>.

#### Example 368

15 (2S)-[5-Bromo-2-(4-tert-butyl-benzenesulfonylamino)-benzoylamino]-3-(2'-p  
 henoxy-biphenyl-4-yl)-propionic acid

A solution of 2-(2-amino-5-bromo-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid (0.06g, 0.11 mmol) [prepared by reacting (2S)-amino-3-(2'-phenoxy-biphenyl-4-yl) propionic acid methyl ester hydrochloride salt and 2-amino-5-bromobenzoic acid by general  
 20 procedure A] ] in CH<sub>2</sub>Cl<sub>2</sub> was treated with of 4-~~ter~~t-butylbenzenesulfonyl chloride (0.025g, 0.11 mmol) according to the general procedure F. Product was purified by flash column chromatography on silicagel using ethyl acetate hexanes to give product as white solid (0.065g, 79.6% yield).

2-[5-Bromo-2-(4-t-butyl-benzenesulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)  
 25 propionic acid methyl ester (0.04g, 0.054 mmol ) was treated with LiOH (2eq, 1N aqueous solution) according to the general procedure C to give 0.034g (87.0%) of 2-[5-Bromo-2(4-t-butyl-benzenesulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl) propionic acid.

<sup>1</sup>HNMR (400MHz, DMSO-*d*<sub>6</sub>): 1.2 (s, 9H) 3.04 (dd, 1H), 3.21 (dd, 1H), 4.58-4.70 (m, 1H),  
 6.83-6.87 (m, 2H), 6.94-6.99 (m, 2H), 7.20-7.39 (m, 6H), 7.42-7.49 (m, 4H), 7.51-7.56 (m,  
 30 2H), 7.64-7.72 (m, 3H), 7.86 (d, 1H), 9.29 (d, 1H), 11.38 (s, 1H), 13.06 (s, 1H)

LC/MS (*m/z*): 727.1 (M+1)<sup>+</sup>.

#### Example 369

35 (2S)-[5-Bromo-2-(4-tert-butyl-benzenesulfonylamino)-benzoylamino]-3-(4'-p  
 henoxy-biphenyl-4-yl)-propionic acid

To a mixture of (L)-4-bromophenylalanine (8.55, 35.0 mmol), 2-phenoxyphenyl boronic acid (10.00g, 46.73 mmol), and palladium tetrakis-triphenylphosphine (4.0 g, 10% mmol) were added DME (140 mL) and 2N Na<sub>2</sub>CO<sub>3</sub> aq. solution (70 mL, 140 mmol). The resulting mixture was heated at 90 °C under N<sub>2</sub> for 20h. While the reaction solution was hot, the aqueous layer was removed and the top organic layer was concentrated. The residue was neutralized with HCl and washed with diethyl ether, and then was dissolved in methanol and the insoluble solid was removed by filtration. The methanol filtrate was refluxed with HCl/Ether for 6 h. After removal of solvents, the solid was washed with ether to afford (2S)-amino-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester in HCl salt form (11.0 g, 28.65 mmol, 82% yield).

(2S)-amino-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester (192 mg, 0.5 mmol) was reacted with 5-bromoanthranilic acid (110 mg, 0.5 mmol) as described in general procedure A. The resulting crude compound was sulfonylated by 4-*tert*-butylbenzenesulfonyl chloride (175 mg, 0.75 mmol) as described in general procedure F. The resulting compound was hydrolyzed according to general procedure C to afford the title product (219 mg, 60%) as a white solid. <sup>1</sup>H-NMR(400 MHz, CDCl<sub>3</sub>): 1.25 (s, 9H), 3.25 (dd, 1H), 3.35 (dd, 1H), 5.01 (dd, 1H), 6.62 (d, 1H), 7.05-7.03 (m, 4H), 7.12 (t, 1H), 7.21 (d, 2H), 7.45-7.33 (m, 6H), 7.54-7.49 (m, 5H), 7.60 (d, 2H), 10.61(s, 1H) LC/MS (*m/z*): 727(M+1)<sup>+</sup>.

#### Example 370

3-Biphenyl-4-yl-(2S)-[2-(3,4-dichloro-benzenesulfonylamino)-5-iodo-benzoylamino]-propionic acid

To the resin-bound L-biphenylalanine (1.2 mmol) which was made in example 279, a solution of 2-amino-5-iodo benzoic acid (3.0 mmol), HOBt (30 mmol), DIC (30 mmol) and DMAP (0.03 mmol) in DMF (30mL) were added and the mixture was shaken overnight. The reaction mixture was drained and washed with DMF, methanol and DCM (3x 150mL each solvent).

To the resin-bound (2S)-(2-amino-5-iodo-benzoylamino)-3-biphenyl-4-yl-propionic acid (0.12mmol) was added a solution of 3,4-dichloro benzenesulfonyl chloride (0.3mmol) and pyridine (0.3 mmol) in 5 ml of DCM and the mixture agitated for 24 hours. The reaction mixture was drained and washed with DMF, methanol and DCM (3x 5mL each solvent).

Resin bound 3-Biphenyl-4-yl-(2S)-[2-(3,4-dichloro-benzenesulfonylamino)-5-iodo-benzoylamino]-propionic acid was treated with 20% TFA in DCM (2mL) for 1 hour. The filtrate was collected and evaporated to give 10 mg of the title compound with 95% purity. LC/MS (*m/z*): 695 (*m* +1)<sup>+</sup>

## Example 371

(2S)-{2-[(Biphenyl-4-sulfonyl)-(4-methyl-benzyl)-amino]-5-chloro-benzoylamino}-3-biphenyl-4-yl-propionic acid

To the resin-bound 3-Biphenyl-4-yl-(2S)-[5-chloro-2-(4-methyl-benzylamino)-benzoylamino]-propionic acid (0.12mmol) prepared in example 358 was added a solution of biphenyl-4-sulfonyl chloride (0.3mmol) and pyridine (0.3 mmol) and the mixture agitated for 72 hours. The reaction mixture was drained and washed with DMF, methanol and DCM (3x 5mL each solvent).

Resin bound (2S)-{2-[(biphenyl-4-sulfonyl)-(4-methyl-benzyl)-amino]-5-chloro-benzoylamino}-3-biphenyl-4-yl-propionic acid was treated with 20% TFA in DCM (2mL) for 1 hour. The filtrate was collected and evaporated to give 10 mg of the title compound with 95% purity. LC/MS (*m/z*): 715 (*m* + 1)<sup>+</sup>

By analogous methods to those described above the following compounds were synthesized.

EXAMPLE	NAME	LC/MS( <i>m/z</i> )
372	(2S)-[2-(Biphenyl-4-sulfonylamino)-5-chloro-benzoylamino]-3-biphenyl-4-yl-propionic acid	611
373	3-Biphenyl-4-yl-(2S)[2-(4-tert-butyl-benzenesulfonylamino)-5-iodo-benzoylamino]-propionic acid	683
374	3-Biphenyl-4-yl-(2S)[[4-(4-tert-butyl-benzenesulfonylamino)-3'-chloro-4'-fluoro-biphenyl-3-carbonyl]-amino]-propionic acid	685
375	3-Biphenyl-4-yl-(2S)[5-iodo-2-(2,4,5-trichloro-benzenesulfonylamino)-benzoylamino]-propionic acid	729
376	3-Biphenyl-4-yl-(2S)-[2-(2,5-dichloro-benzenesulfonylamino)-5-iodo-benzoylamino]-propionic acid	695
377	3-Biphenyl-4-yl-(2S)-[2-(2,4-difluoro-benzenesulfonylamino)-5-iodo-benzoylamino]-propionic acid	663

EXAMPLE	NAME	LC/MS(m/z)
378	3-Biphenyl-4-yl-(2S)-[5-iodo-2-(4-propyl-benzenesulfonylamino)-benzoylamino]-propionic acid	
379	3-Biphenyl-4-yl-(2S)-(5-iodo-2-pentamethylbenzenesulfonylamino-benzoylamino)-propionic acid	697
380	3-Biphenyl-4-yl-(2S)-[5-iodo-2-(toluene-4-sulfonylamino)-benzoylamino]-propionic acid	
381	3-Biphenyl-4-yl-(2S)-[2-(4-bromo-benzenesulfonylamino)-5-iodo-benzoylamino]-propionic acid	706
382	3-Biphenyl-4-yl-(2S)-[5-iodo-2-(naphthalene-2-sulfonylamino)-benzoylamino]-propionic acid	677
383	3-Biphenyl-4-yl-(2S)-[5-bromo-2-(4-tert-butyl-benzenesulfonylamino)-benzoylamino]-propionic acid	636
384	2-[5-Acetylamino-(2S)-(4-tert-butyl-benzenesulfonylamino)-benzoylamino]-3-biphenyl-4-yl-propionic acid	614
385	3-Biphenyl-4-yl-(2R)-[5-bromo-2-(4-tert-butyl-benzenesulfonylamino)-benzoylamino]-propionic acid methyl ester	650
386	3-Biphenyl-4-yl-(2S)-[5-bromo-2-(6-morpholin-4-yl-pyridine-3-sulfonylamino)-benzoylamino]-propionic acid	665
387	3-Biphenyl-4-yl-(2S)-[5-bromo-2-(4-vinyl-benzenesulfonylamino)-benzoylamino]-propionic acid	606
388	3-Biphenyl-4-yl-(2S)-[5-bromo-2-(3,4-dichloro-benzenesulfonylamino)-benzoylamino]-propionic acid	648

EXAMPLE	NAME	LC/MS(m/z)
389	3-Biphenyl-4-yl-(2S)-[5-bromo-2-(4-nitro-benzenesulfonylamino)-benzoylamino]-propionic acid	625
390	3-Biphenyl-4-yl-(2S)-[5-bromo-2-(2-phenyl-ethenesulfonylamino)-benzoylamino]-propionic acid	608
391	3-Biphenyl-4-yl-(2S)-[5-bromo-2-[5-(5-trifluoromethyl-isoxazol-3-yl)-thiophene-2-sulfonylamino]-benzoylamino]-propionic acid	721
392	3-Biphenyl-4-yl-(2S)-[5-bromo-2-(4-bromo-benzenesulfonylamino)-benzoylamino]-propionic acid	659
393	3-Biphenyl-4-yl-(2S)-[5-bromo-2-(3,4-dimethoxy-benzenesulfonylamino)-benzoylamino]-propionic acid	640
394	(2S)-[2-(4-Acetylamino-benzenesulfonylamino)-5-bromo-benzoylamino]-3-biphenyl-4-yl-propionic acid	637
395	3-Biphenyl-4-yl-(2S)-[5-bromo-2-(4-isopropyl-benzenesulfonylamino)-benzoylamino]-propionic acid	622
396	3-Biphenyl-4-yl-(2S)-[5-bromo-2-(2,5-dichloro-benzenesulfonylamino)-benzoylamino]-propionic acid	648
397	3-Biphenyl-4-yl-(2S)-[5-bromo-2-(2-trifluoromethoxy-benzenesulfonylamino)-benzoylamino]-propionic acid	664
398	(2S)-[5-Bromo-2-(5-dibutylamino-naphthalene-1-sulfonylamino)-benzoylamino]-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid	849

EXAMPLE	NAME	LC/MS(m/z)
399	(2S)-[5-Chloro-2-(5-dibutylamino-naphthalene-1-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	804
400	(2S)-[5-Chloro-2-(5-dimethylamino-naphthalene-1-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	734
401	(2S)-[5-Bromo-2-(5-dimethylamino-naphthalene-1-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	780
402	(2S)-[5-Chloro-2-(5-dimethylamino-naphthalene-1-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	720
403	(2S)-[5-Bromo-2-(5-dimethylamino-naphthalene-1-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	765
404	(2S)-[5-Bromo-2-(5-dibutylamino-naphthalene-1-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	849
405	(2S)-(2-Benzenesulfonylamino-5-chloro-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	641
406	(2S)-(2-Benzenesulfonylamino-5-chloro-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	627
407	(2S)-[5-Chloro-2-(naphthalene-1-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	691



EXAMPLE	NAME	LC/MS(m/z)
408	(2S)-[5-Chloro-2-(naphthalene-1-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	677
409	(2S)-[5-Chloro-2-(naphthalene-2-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	691
410	(2S)-[5-Chloro-2-(naphthalene-2-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	677
411	(2S)-[2-(4-tert-Butyl-benzenesulfonylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	697
412	(2S)-[2-(4-tert-Butyl-benzenesulfonylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	683
413	(2S)-[2-(Biphenyl-4-sulfonylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	717
414	(2S)-[2-(Biphenyl-4-sulfonylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	703
415	(2S)-[5-Chloro-2-(quinoline-8-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	692
416	(2S)-[5-Chloro-2-(quinoline-8-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	678

EXAMPLE	NAME	LC/MS(m/z)
417	(2S)-[5-Chloro-2-(5-chloro-1,3-dimethyl-1H-pyrazole-4-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	679
418	(2S)-[5-Chloro-2-(1-methyl-1H-imidazole-4-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	631
419	(2S)-[5-Chloro-2-(6-phenoxy-pyridine-3-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	720
420	(2S)-[5-Chloro-2-(4-pyrazol-1-yl-benzenesulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	693
421	(2S)-[5-Chloro-2-(5-chloro-1,3-dimethyl-1H-pyrazole-4-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	693
422	(2S)-[5-Chloro-2-[3-(5-methyl-[1,3,4]oxadiazol-2-yl)-benzenesulfonylamino]-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	723
423	(2S)-[5-Chloro-2-(6-phenoxy-pyridine-3-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	734
424	(2S)-[5-Chloro-2-(4-pyrazol-1-yl-benzenesulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	707
425	(2S)-[5-Chloro-2-(1-methyl-1H-imidazole-4-sulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	645

EXAMPLE	NAME	LC/MS(m/z)
426	(2S)-[5-Chloro-2-(3,5-dimethyl-isoxazole-4- sulfonylamino)-benzoylamino]-3-(2'- phenoxy-biphenyl-4-yl)-propionic acid ethyl ester	660
427	(2S)-[5-Chloro-2-(6-morpholin-4-yl-pyridine- 3-sulfonylamino)-benzoylamino]-3-(2'- phenoxy-biphenyl-4-yl)-propionic acid methyl ester	727
428	(2S)-[5-Chloro-2-(6-morpholin-4-yl-pyridine- 3-sulfonylamino)-benzoylamino]-3-(2'- phenoxy-biphenyl-4-yl)-propionic acid	713
429	(2S)-[5-Chloro-2-[5-(2-methylsulfanyl- pyrimidin-4-yl)-thiophene-2-sulfonylamino]- benzoylamino]-3-(2'-phenoxy-biphenyl-4- yl)-propionic acid methyl ester	771
430	(2S)-[5-Chloro-2-[5-(2-methylsulfanyl- pyrimidin-4-yl)-thiophene-2-sulfonylamino]- benzoylamino]-3-(2'-phenoxy-biphenyl-4- yl)-propionic acid	757
431	(2S)-[5-Chloro-2-[4-(5-methyl- [1,3,4]oxadiazol-2-yl)- benzenesulfonylamino]-benzoylamino]-3- (2'-phenoxy-biphenyl-4-yl)-propionic acid	709
432	3-Biphenyl-4-yl-(2S)-[2-(2,5-dichloro- benzenesulfonylamino)-5-iodo- benzoylamino]-propionic acid methyl ester	709
433	3-Biphenyl-4-yl-(2S)-[2-(4-bromo- benzenesulfonylamino)-5-iodo- benzoylamino]-propionic acid methyl ester	720
434	3-Biphenyl-4-yl-(2S)-[2-(3,5-bis- trifluoromethyl-benzenesulfonylamino)-5- chloro-benzoylamino]-propionic acid	671

EXAMPLE	NAME	LC/MS(m/z)
435	(2S)-[5-Chloro-2-(4-oxazol-5-yl-benzenesulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	708
436	(2S)-[5-Chloro-2-(4-oxazol-5-yl-benzenesulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	694
437	(2S)-[5-Chloro-2-(4-phenoxy-benzenesulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	733
438	(2S)-[5-Chloro-2-(4-phenoxy-benzenesulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	719
439	(2S)-[5-Chloro-2-(3-nitro-benzenesulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	672
440	(2S)-[2-(3,5-Bis-trifluoromethyl-benzenesulfonylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	777
441	(2S)-[2-(3,5-Bis-trifluoromethyl-benzenesulfonylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	763
442	(2S)-[2-(3-Amino-benzenesulfonylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	656
443	(2S)-{5-Chloro-2-[5-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yl)-thiophene-2-sulfonylamino]-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	795

EXAMPLE	NAME	LC/MS(m/z)
444	(2S)-{5-Chloro-2-[5-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yl)-thiophene-2-sulfonylamino]-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	781
445	3-Biphenyl-4-yl-(2S)-[5-chloro-2-(5-dibutylamino-naphthalene-1-sulfonylamino)-benzoylamino]-propionic acid methyl ester	726
446	3-Biphenyl-4-yl-(2S)-[5-chloro-2-(5-dibutylamino-naphthalene-1-sulfonylamino)-benzoylamino]-propionic acid	712
447	(2S)-[5-Bromo-2-(4-tert-butyl-benzenesulfonylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	742
448	(2S)-[5-Bromo-2-(4-tert-butyl-benzenesulfonylamino)-benzoylamino]-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester	742
449	3-Biphenyl-4-yl-(2S)-{5-chloro-2-[naphthalen-1-ylmethyl-(4-nitro-benzenesulfonyl)-amino]-benzoylamino}-propionic acid	720
450	(2S)-{2-[(Biphenyl-4-sulfonyl)-(3-methylthiophen-2-ylmethyl)-amino]-5-chloro-benzoylamino}-3-biphenyl-4-yl-propionic acid	721
451	(2S)-{2-[(Biphenyl-4-sulfonyl)-(3-phenylpropyl)-amino]-5-chloro-benzoylamino}-3-biphenyl-4-yl-propionic acid	729
452	(2S)-{2-[(Biphenyl-4-sulfonyl)-biphenyl-4-ylmethyl-amino]-5-chloro-benzoylamino}-3-biphenyl-4-yl-propionic acid	777

EXAMPLE	NAME	LC/MS(m/z)
453	(2S)-{2-[(Biphenyl-4-sulfonyl)-naphthalen-1-ylmethyl-amino]-5-chloro-benzoylamino}-3-biphenyl-4-yl-propionic acid	751
454	(2S)-{2-[(Biphenyl-4-sulfonyl)-(4-isopropyl-benzyl)-amino]-5-chloro-benzoylamino}-3-biphenyl-4-yl-propionic acid	753
455	3-Biphenyl-4-yl-(2S)-{2-[biphenyl-4-ylmethyl-(2,4-dichloro-benzenesulfonyl)-amino]-5-chloro-benzoylamino}-propionic acid	769
456	(2S)-{2-[(Biphenyl-4-sulfonyl)-ethyl-amino]-5-chloro-benzoylamino}-3-biphenyl-4-yl-propionic acid	639
457	(2S)-{2-[(Biphenyl-4-sulfonyl)-ethyl-amino]-5-iodo-benzoylamino}-3-biphenyl-4-yl-propionic acid	731

## Example 458

2-[5-Chloro-2-[(naphthalen-1-ylmethyl)-amino]-benzoylamino]-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid

5 A solution of 2-amino-5-chlorobenzoic acid (0.58 g, 3.37 mmol) in DMF (7.0 mL) was reacted with (L)-4-bromophenylalanine methyl ester hydrochloride (1.00 g, 3.37 mmol), HBTU (1.20 g, 3.37 mmol), and DIEA (1.80 mL, 10.13 mmol) by the general procedure A. The crude product was purified by flash column chromatography on silica gel using DCM(+50% hexane) followed by DCM to give 0.890 g (64%) of 2-(2-amino-5-chloro-  
10 benzoylamino)-3-(4-bromo-phenyl)-propionic acid methyl ester as a white solid.

A solution of 2-(2-amino-5-chloro-benzoylamino)-3-(4-bromo-phenyl)-propionic acid methyl ester (0.600 g, 1.45 mmol) in DME (10.0 mL) was reacted with 4-trifluoromethylbenzene boronic acid (0.55 g, 2.91 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (0.70 g, 0.14 mmol), and Na<sub>2</sub>CO<sub>3</sub> (2.0 N, 3.50 mL, 3.64 mmol) by the general procedure D to form 0.850 g of 2-(2-amino-5-chloro-  
15 benzoylamino)-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester as a brown oil.

A solution of 2-(2-amino-5-chloro-benzoylamino)-3-(4-bromo-phenyl)-propionic acid methyl ester (0.830 g, 1.74 mol) in DCE (15 mL) was reacted with 1-naphthaldehyde (0.244 g, 3.50 mmol), sodium triacetoxyborohydride (0.553 g, 2.61 mmol), and acetic acid/DCM(1.0 M, 2.0 mL) by the general procedure E. The crude product was purified by flash column

chromatography on silica gel using DCM (+35% hexane) to give 0.580 g (54%) of 2-{5-Chloro-2-[(naphthalen-1-ylmethyl)-amino]-benzoylamino}-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester as a colorless oil. This ester was treated with LiOH (0.123 g, 2.92 mmol) by the general procedure J to give 0.405 g (92%) of the title compound. 2-{5-chloro-2-[(naphthalen-1-ylmethyl)-amino]-benzoylamino}-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid as a white solid. LCMS 603 (M+1)<sup>+</sup>. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) 8.62 [d, 1 H], 8.10 [m, 1 H], 8.03 [m, 1 H], 7.92 [m, 1 H], 7.81 [m, 2 H], 7.72 [m, 2 H], 7.59 [m, 3 H], 7.50 [m, 2 H], 7.38 [m, 3 H], 7.23 [dd, 1 H], 6.67 [d, 1 H], 4.47 [m, 1 H], 3.25 [dd, 1 H], 3.16 [s, 2 H], 3.07 [m, 1 H].

#### Example 459

(2S)-(2-[3-(4-tert-Butyl-phenoxy)-benzylamino]-5-chloro-benzoylamino)-3-(4'-cyclohexyl-biphenyl-4-yl)-propionic acid

(2S)-(2-Amino-5-chloro-benzoylamino)-3-biphenyl-4-yl-propionic acid methyl ester was prepared following General Procedure A using 2-amino-5-chloro-benzoic acid (1.751 g, 98%, 10 mmol), (S)-2-amino-3-(4-bromo-phenyl)-propionic acid methyl ester hydrochloride salt (2.95 g, 10 mmol), HBTU (4.55 g, 12 mmol) and DIEA (6.33 mL, 99%, 36 mmol) in DMF (60 mL). Purification by flash chromatography (ethyl acetate/hexanes 1:3, 1:2, 1:1.5) gave solid (3.48 g, 8.45 mmol, 85% yield).

(2S)-(2-Amino-5-chloro-benzoylamino)-3-(4'-cyclohexyl-biphenyl-4-yl)propionic acid methyl ester compound was prepared following General Procedure D using (S)-2-(2-amino-5-chloro-benzoylamino)-3-(4-bromo-phenyl)-propionic acid methyl ester (1.803 g, 4.38 mmol), 4-cyclohexyl-benzene boronic acid (1.61 g, 98%, 7.88 mmol), palladium tetrakis-triphenylphosphine (0.462 g, 0.4 mmol), and aqueous Na<sub>2</sub>CO<sub>3</sub> (2.0 N, 16 mL, 32 mmol) in DME (32 mL). The mixture was heated at 80 °C for 14 h. Purification by flash chromatography (ethyl acetate/hexanes 1:3, 1:2) gave product as a red solid (2.01 g, 4.09 mmol, 93% yield).

Reductive amination was carried out using (2S)-(2-amino-5-chloro-benzoylamino)-3-(4'-cyclohexyl-biphenyl-4-yl)propionic acid methyl ester (123 mg, 0.25 mmol), 3-(4-tert-butyl-phenoxy)-benzaldehyde (130 mg, 98%, 0.5 mmol), acetic acid (0.7 mmol), sodium triacetoxyborohydride (131 mg, 97%, 0.6 mmol) and DCE (2.5 mL). The mixture was stirred for 7 h. Purification by flash chromatography (ethyl acetate/hexanes 1:9) gave the title compound as colorless oil (139 mg, 0.19 mmol, 76% yield).

The title compound was prepared following General Procedure C using (S)-2-(2-[3-(4-tert-Butyl-phenoxy)-benzylamino]-5-chloro-benzoylamino)-3-(4'-cyclohexyl-biphenyl-4-yl)-propionic acid methyl ester (135 mg, 0.19 mmol), LiOH<sub>(aq)</sub> (2.0 N, 0.22 mL, 0.44 mmol), THF

(4 mL) and MeOH (1 mL). The mixture was stirred at 0 °C for 12 h. The product was obtained as off-white solid (115 mg, 0.16 mmol, 84% yield).

<sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>): 12.82 (s, 1H), 8.77(d, 1H), 8.06(t, 1H), 7.62(d, 1H), 6.75-7.54(m, 17H), 6.54(d, 1H), 4.59(ddd, 1H), 4.33(d, 2H), 3.08-3.31(m, 3H), 1.33-1.79(m, 10H), 1.24(s, 9H); LC-MS *m/z*: 715 (M+1)<sup>+</sup>.

#### Example 460

(2S)-{5-Chloro-2-[(naphthalen-1-ylmethyl)-amino]-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

2-Amino-5-chlorobenzoic acid methyl ester (1.85g, 10.0 mmol) was treated with 1-naphthaldehyde (1.56g, 10.0 mmol) and sodium triacetoxyborohydride (4.23g, 20.0 mmol) in 1,2-dichloroethane as described in general procedure E to give 5-chloro-2-[(naphthalen-1-ylmethyl)-amino]-benzoic acid methyl ester (2.54g, 78%). This methyl ester (2.0g, 6.13 mmol) was treated with LiOH (2eq, 1N aqueous solution) according to the general procedure C gave 5-chloro-2-[(naphthalen-1-yl-methyl)-amino]-benzoic acid (1.64g, 86.0 %).

5-Chloro-2-[(naphthalen-1-yl-methyl)-amino]-benzoic acid (0.1g, 0.32 mmol) was treated with (2S)-amino-3-(2'-phenoxy-biphenyl-4-yl) propionic acid methyl ester hydrochloride salt (0.123g, 0.32mmol) according to the general procedure A to give 2-{5-Chloro-2-[(naphthalene-1-yl-methyl)-amino]-3-(2'phenoxy-biphenyl-4-yl)-propionic acid methyl ester (.155g, 75.6%). This methyl ester (0.15g, 0.23 mmol) was treated with LiOH (2eq, 1N aqueous solution) according to the general procedure C to give 2-{5-chloro-2-[(naphthalene-1-yl-methyl)-amino]-3-(2'phenoxy-biphenyl-4-yl)-propionic acid (0.13g, 90.0%) as white solid. <sup>1</sup>HNMR (400MHz, DMSO-*d*<sub>6</sub>): 3.36 (dd, 1H), 3.46 (dd, 1H), 4.79-4.88 (m, 1H), 5.10 (d, 2H), 7.01 (d, 1H), 7.18 (d, 2H), 7.26(d, 1H), 7.33 (t, 1H), 7.50-7.90(m, 14H), 7.96(d, 1H), 8.10-8.20 (m, 1H), 8.22-8.30 (m, 1H), 8.32-8.48 (m, 2H), 9.07(d, 1H), 13.10 (s, 1H). LC/MS (*m/z*): 627.2 (M+1)<sup>+</sup>.

#### Example 461

(2S)-{5-Chloro-2-[(naphthalen-2-ylmethyl)-amino]-benzoylamino}-3-(2'-piperidin-1-ylmethyl-biphenyl-4-yl)-propionic acid

The (2S)-(2-Amino-5-chloro-benzoylamino)-3-(4-bromo-phenyl)-propionic acid methyl ester (0.400g, 0.972mmol) was made according to the procedure for Example 282 and this was subjected to reductive amination with naphthalene-2-carbaldehyde (0.227g, 1.45mmol) and sodium triacetoxyborohydride (0.515g, 2.43mmol) as per general procedure E to yield the 3-(4-Bromo-phenyl)-2-{5-chloro-2-[(naphthalen-2-ylmethyl)-amino]-benzoylamino}-propionic acid methyl ester (0.428g, 80%).



The above compound (0.360g, 0.653mmol) was then subjected to Suzuki coupling with 2-(formylphenyl) boronic acid (0.195g, 1.306mmol) and Pd (PPh<sub>3</sub>) (0.075g, 0.0653 mmol) and 2N Na<sub>2</sub>CO<sub>3</sub> (2.0ml, 1.956mmol) as per general procedure D to yield (2S)-{5-Chloro-2- [(naphthalen-2-ylmethyl)-amino]-benzoylamino}-3-(2'-formyl-biphenyl-4-yl)-propionic acid methyl ester (0.244g, 65%).

The title compound was hen prepared by reductive amination on (2S)-{5-chloro-2- [(naphthalen-2-ylmethyl)-amino]-benzoylamino}-3-(2'-formyl-biphenyl-4-yl)-propionic acid methyl ester (0.100g, 0.173mmol) with piperidine (0.0345g, 0.347mmol) as per general procedure E to give the (2S)-{5-chloro-2- [(naphthalen-2-ylmethyl)-amino]-benzoylamino}-3-(2'-piperidin-4-ylmethyl-biphenyl-4-yl)-propionic acid methyl ester which was further hydrolyzed as per general procedure C to give the title compound (0.56g, 50%). LC/MS (m/z): 632(M+1).

By analogous methods to those described above the following compounds were synthesized.

EXAMPLE	NAME	LC/MS (m/z)
462	2S-[5-Chloro-2-(2-methyl-butylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	557
463	3-Biphenyl-4-yl-2S-[5-chloro-2-[(naphthalen-1-ylmethyl)-amino]-benzoylamino]-propionic acid	535
464	3-(4'-tert-Butyl-biphenyl-4-yl)-(2S)-{5-chloro-2-[(naphthalen-1-ylmethyl)-amino]-benzoylamino}-propionic acid	591
465	(2S)-{5-Chloro-2-[(naphthalen-1-ylmethyl)-amino]-benzoylamino}-3-(4'-methanesulfonyl-biphenyl-4-yl)-propionic acid	613
466	(2S)-{5-Chloro-2-hexylamino-benzoylamino}-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid	547
467	(2S)-{5-Chloro-2-hexylamino-benzoylamino}-3-(4'-dimethylamino-biphenyl-4-yl)-propionic acid	522

EXAMPLE	NAME	LC/MS (m/z)
468	(2S)-[2-(4-tert-Butyl-benzylamino)-5-chloro-benzoylamino]-3-(4'-dimethylamino-biphenyl-4-yl)-propionic acid	584
469	(2S)-{2-[3-(4-tert-Butyl-phenoxy)-benzylamino]-5-chloro-benzoylamino}-3-(4'-dimethylamino-biphenyl-4-yl)-propionic acid	676
470	(2S)-{5-Chloro-2-[(naphthalen-1-ylmethyl)-amino]-benzoylamino}-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid	627
471	(2S)-[2-(4-tert-Butyl-benzylamino)-5-chloro-benzoylamino]-3-(4'-cyclohexyl-biphenyl-4-yl)-propionic acid	623
472	(2S)-(5-Chloro-2-heptylamino-benzoylamino)-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid	585
473	(2S)-(5-Chloro-2-heptylamino-benzoylamino)-3-(4'-cyclohexyl-biphenyl-4-yl)-propionic acid	575
474	(2S)-{5-Chloro-2-[(naphthalen-1-ylmethyl)-amino]-benzoylamino}-3-(4'-cyclohexyl-biphenyl-4-yl)-propionic acid	617
475	(2S)-{5-Chloro-2-[(naphthalen-1-ylmethyl)-amino]-benzoylamino}-3-(4'-pentyl-biphenyl-4-yl)-propionic acid	605
476	(2S)-[2-(4-tert-Butyl-benzylamino)-5-iodo-benzoylamino]-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid	725
477	3-(4'-Amino-biphenyl-4-yl)-2S-{5-chloro-2-[(naphthalen-1-ylmethyl)-amino]-benzoylamino}-propionic acid	550

EXAMPLE	NAME	LC/MS (m/z)
478	3-Biphenyl-4-yl-2S-[2-(4-tert-butyl-benzylamino)-5-(3,4-dichloro-phenoxy)-benzoylamino]-propionic acid	667
479	3-Biphenyl-4-yl-2S-[2-(4-tert-butyl-benzylamino)-5-(3-chloro-4-fluoro-phenoxy)-benzoylamino]-propionic acid	651
480	3-Biphenyl-4-yl-(2S)-[2-(4-tert-butyl-benzylamino)-5-(3-trifluoromethyl-phenoxy)-benzoylamino]-propionic acid	667
481	3-Biphenyl-4-yl-(2S)-[2-(4-tert-butyl-benzylamino)-5-(2,3,4-trichloro-phenoxy)-benzoylamino]-propionic acid	701
482	3-Biphenyl-4-yl-(2S)-[2-(4-tert-butyl-benzylamino)-4-chloro-benzoylamino]-propionic acid	541
483	3-Biphenyl-4-yl-(2S)-[2-(4-tert-butyl-benzylamino)-5-(4-chloro-phenoxy)-benzoylamino]-propionic acid	633
484	3-Biphenyl-4-yl-2S-[2-(4-tert-butyl-benzylamino)-5-(4-chloro-3-fluoro-phenoxy)-benzoylamino]-propionic acid	651
485	3-Biphenyl-4-yl-(2S)-[2-(4-tert-butyl-benzylamino)-5-(3,4-dimethoxy-phenoxy)-benzoylamino]-propionic acid	659
486	3-(2'-Benzyloxy-biphenyl-4-yl)-(2S)-[5-chloro-2-[(naphthalen-1-ylmethyl)-amino]-benzoylamino]-propionic acid	641
487	3-(3'-Benzyloxy-biphenyl-4-yl)-(2S)-[5-chloro-2-[(naphthalen-1-ylmethyl)-amino]-benzoylamino]-propionic acid	641

EXAMPLE	NAME	LC/MS (m/z)
488	(2S)-{5-Chloro-2-[(naphthalen-1-ylmethyl)-amino]-benzoylamino}-3-(2'-trifluoromethyl-biphenyl-4-yl)-propionic acid	603
489	(2S)-{2-[3-(4-tert-Butyl-phenoxy)-benzylamino]-5-chloro-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	725
490	(2S)-[2-(4-tert-Butyl-benzylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	633
491	(2S)-[5-Bromo-2-(4-tert-butyl-benzylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	678
492	(2S)-[5-Bromo-2-(2-methyl-pentylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	616
493	3-Biphenyl-4-yl-(2S)-{5-chloro-2-[(piperidin-4-ylmethyl)-amino]-benzoylamino}-propionic acid	492
494	3-(2'-Benzyloxy-biphenyl-4-yl)-(2S)-{2-[3-(4-tert-butyl-phenoxy)-benzylamino]-5-chloro-benzoylamino}-propionic acid	739
495	3-(2'-Benzyloxy-biphenyl-4-yl)-(2S)-[2-(4-tert-butyl-benzylamino)-5-chloro-benzoylamino]-propionic acid	647
496	(2S)-[5-Chloro-2-(3-phenoxy-benzylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	669
497	(2S)-[2-(3,5-Bis-trifluoromethyl-benzylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	713

EXAMPLE	NAME	LC/MS (m/z)
498	(2S)-[5-Chloro-2-(4-phenoxy-benzylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	669
499	(2S)-[2-(4-Benzoyloxy-benzylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	683
500	3-Biphenyl-4-yl-(2S)-[5-(2-chloro-4-trifluoromethyl-phenoxy)-2-(2-methyl-butylamino)-benzoylamino]-propionic acid	625
501	(2S)-[3,5-Dichloro-2-(2-methyl-butylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	591
502	(2S)-[5-Bromo-2-(cyclohexylmethyl-amino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	628
503	(2S)-(5-Chloro-2-pentylamino-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	557
504	(2S)-{2-[3-(4-tert-Butyl-phenoxy)-benzylamino]-5-chloro-benzoylamino}-3-(2'-hydroxy-biphenyl-4-yl)-propionic acid	649
505	(2S)-(5-Chloro-2-hexa-2,4-dienylamino-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	567
506	(2S)-[5-Chloro-2-(3-phenyl-propylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	605
507	(2S)-(5-Chloro-2-octylamino-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	599

EXAMPLE	NAME	LC/MS (m/z)
508	(2S)-(5-Chloro-2-hexylamino-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	571
509	(2S)-[5-Chloro-2-(2,2-dimethyl-propylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	557
510	(2S)-[5-Chloro-2-(2-methyl-pent-2-enylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	569
511	(2S)-(5-Chloro-2-ethylamino-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	515

## Example 512

(2S)-(5-Chloro-2-diethylamino-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid  
 5 (2S)-(2-Amino-5-chloro-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester was prepared (0.6 g, 80%) from (2S)-Amino-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester (0.5g, 1.5 mmol), 5-chloro-2-amino-benzoic acid (0.28g, 1.65 mmol) as described in general procedure A.

10 (2S)-(2-Amino-5-chloro-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester (0.5g, 1.0 mmol), was reacted with acetaldehyde (0.175 g, 3.0 mmol), sodium cyanoboro hydride (10 ml 1.0M solution in THF, 10 mmol), in DCM (50 ml) as described in the general procedure E. The crude product was purified by flash column chromatography on silica gel using DCM as an eluent to give ester which was hydrolyzed by following the  
 15 general procedure I to give 0.4 g (69% of over all) of the title compound. LCMS: 543 (M+1)<sup>+</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) [t, 6H], 2.88 [q, 4 H], 3.45 [m, 1H], 3.58 [m, 1 H], 5.12 [m, 1H], 7.17-7.7 [m, 16 H], 8.48 [d, 1 H], 11.57 [s, 1 H].

## Example 513

20 2-(5-Chloro-2-diethylamino-benzoylamino)-3-[3'-(4-trifluoromethyl-phenoxy)-biphenyl-4-yl]-propionic acid

A solution of (L)-4-bromophenylalanine (7.0 g, 28.6 mmol) in DME(100 mL) was reacted with 3-hydroxyphenyl boronic acid(5.14 g, 37.2 mmol), palladium tetrakis-

triphenylphosphine (3.3 g, 2.8 mmol), and  $\text{Na}_2\text{CO}_3$  (2.0 N, 43.0 mL, 86 mmol) by the general procedure D. After removal of solvent, the solid was washed with ether and DCM to afford 2-amino-3-(3'-hydroxy-biphenyl-4-yl)propionic acid methyl ester in HCl salt form (8.20 g, 31.9 mmol, 93% yield).

5 A solution of 2-amino-5-chloro-benzoic acid (1.95 g, 11.38 mmol) in DMF (10.0 mL) was reacted with 2-amino-3-(3'-hydroxy-biphenyl-4-yl)propionic acid methyl ester (3.50 g, 11.38 mmol), HBTU (3.98 g, 10.50 mmol), and DIEA (6.08 mL, 34.15 mmol) by the general procedure A. The crude product was purified by flash column chromatography on silica gel using DCM (+15% hexane) and increasing the gradient to DCM and finally DCM (+0.25% methanol) to give 1.75 g, (36%) of 2-(2-amino-5-chloro-benzoylamino)-3-(3'-hydroxy-biphenyl-4-yl)propionic acid methyl ester as a white solid. LCMS: 425 ( $M+1$ )<sup>+</sup>.

10 A solution 2-(2-amino-5-chloro-benzoylamino)-3-(3'-hydroxy-biphenyl-4-yl)propionic acid methyl ester (0.850 g, 2.00 mmol) was reacted with acetaldehyde (0.350 g, 6.01 mmol), sodium triacetoxyborohydride (0.850 g, 4.00 mmol), and acetic acid/DCM (1.0 M, 3.00 mL) by the general procedure E. The crude product was purified by flash column chromatography on silica gel using DCM (+15% hexane) and increasing the gradient to DCM and finally DCM (+0.25% methanol) to give 0.540 g, (56%) of the phenolic ester.

15 A solution of this phenolic ester (0.240 g, 0.49 mmol) in DCM (5.0 mL) was reacted with copper acetate (0.100 g, 0.54 mmol), and 4-trifluoromethylbenzene boronic acid (0.236 g, 1.24 mmol), and triethyl amine (0.350 mL) by the general procedure G. The crude product was purified by the flash column chromatography on silica gel using DCM (+5% hexane) to give 0.133 g, (43%) of 2-(5-Chloro-2-diethylamino-benzoylamino)-3-[3'-(4-trifluoromethyl-phenoxy)-biphenyl-4-yl]-propionic acid methyl ester. This ester (0.110 g, 0.17 mmol) was reacted with LiOH (0.030 g, 0.70 mmol) by the general procedure J to give 0.095 g (89%) of 2-(5-Chloro-2-diethylamino-benzoylamino)-3-[3'-(4-trifluoromethyl-phenoxy)-biphenyl-4-yl]-propionic acid as a white solid. LCMS: 612 ( $M+1$ )<sup>+</sup>. <sup>1</sup>H NMR ( $\text{CDCl}_3$ ) 11.56 [s, 1 H], 8.28 [d, 1 H], 7.59 [d, 2 H], 7.42 [dd, 1 H], 7.35 [dd, 1 H], 7.28 [m, 4 H], 7.19 [t, 1 H], 7.15 [d, 1 H], 7.09 [d, 1 H], 7.02 [dd, 1 H], 7.00 [dd, 1 H], 5.05 [m, 1 H], 3.32 [m, 2 H], 2.79 [q, 4 H], 0.69 [t, 6 H].

#### 30 Example 514

35 To a solution of 5-chloro-2-fluoro-benzonitrile (0.700 g, 4.499 mmol) in anhydrous DMF (8.0 mL) was added 3,5-dimethylpiperidine (0.713 g, 6.299 mmol) and cesium carbonate (4.30 g, 13.497 mmol). The reaction mixture was heated at 80 C for 2 h. Upon cooling to rt, water and ethylacetate was added. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. To the combined organic layer was

added ether and the organic layer was washed with water and brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure to give 1.15 g(96%) of 5-chloro-2-(3,5-dimethyl-piperidin-1-yl)-benzonitrile as solid. LCMS 249(M+1)<sup>+</sup>. The compound was >98% purity and was hence used directly for the next step

5 To a solution of 5-chloro-2-(3,5-dimethyl-piperidin-1-yl)-benzonitrile (1.05 g, 4.220 mmol) in Diethylene glycol monomethyl ether (2.50 mL) was added KOH (0.947 g, 16.883 mmol) and water (0.750 ml). The reaction was heated at 130-135 °C overnight. Upon cooling to rt, water and ethyl acetate was added. the organic layer was discarded and the aqueous layer is acidified to pH-6-7. The aqueous layer was then extracted with ethyl  
10 acetate three times. The combined organic layer was washed with water, brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated to give required 5-chloro-2-(3,5-dimethyl-piperidin-1-yl)-benzoic acid (0.850 g, 75%) as an off white solid. LCMS 268(M+1)<sup>+</sup>.

A solution of 5-chloro-2-(3,5-dimethyl-piperidin-1-yl)-benzoic acid (0.250 g, 0.933 mmol) in DMF (4.0 mL) was reacted with (2S)-amino-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester hydrochloride (0.360 g, 0.933 mmol), HBTU (0.355 g, 0.933 mmol), and DIEA (0.500 mL, 2.800 mmol) by the general procedure A. The crude product was purified by flash column chromatography on silica gel using DCM(+20% hexane) to give 0.435 g (62%) of 2-[5-Chloro-2-(3,5-dimethyl-piperidin-1-yl)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester. A solution of this ester (0.200 g, 0.334 mmol) in THF (4.0  
20 mL) was reacted with LiOH (0.050 g, 1.172 mmol) by the general procedure I to give 0.182 g (93%) of 2-[5-Chloro-2-(3,5-dimethyl-piperidin-1-yl)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid as a white solid. LCMS: 584 (M+1)<sup>+</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 11.20 [d, 1 H], 8.21 [d, 1H], 7.45 [m, 2 H], 7.39[m, 2 H], 7.23 [m, 8 H], 7.02 [m, 2 H], 6.86 [m, 2 H], 4.90 [m, 1 H], 3.38 [dd, 5.60 Hz, 1 H], 3.26 [dd, 1 H], 2.80 [m, 2 H], 2.16 [t, 1 H], 2.04 [t, 1 H], 1.70 [m,  
25 2 H], 1.43 [m, 1 H], 0.76 [m, 6 H], 0.58 [m, 1 H].

By analogous methods to those described above the following compounds were synthesized.

EXAMPLE	NAME	LC/MS(m/z)
515	3-Biphenyl-4-yl-(2S)-{2-[bis-(4-benzyloxy-benzyl)-amino]-5-chloro-benzoylamino}-propionic acid	787
516	3-Biphenyl-4-yl-(2S)-[2-(bis-naphthalen-1-ylmethyl-amino)-5-chloro-benzoylamino]-propionic acid	675



EXAMPLE	NAME	LC/MS(m/z)
517	3-Biphenyl-4-yl-(2S)-[2-(bis-biphenyl-4-ylmethyl-amino)-5-chloro-benzoylamino]-propionic acid	727
518	(2S)-(5-Bromo-2-dibutylamino-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	644
519	(2S)-(5-Bromo-2-dihexylamino-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	700
520	(2S)-(5-Chloro-2-dipentylamino-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	627
521	(2S)-(5-Chloro-2-piperidin-1-yl-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	555
522	(2S)-(5-Bromo-2-diethylamino-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	588
523	(2S)-(5-Chloro-2-diethylamino-benzoylamino)-3-[3'-(3-chloro-4-fluoro-phenoxy)-biphenyl-4-yl]-propionic acid	595
524	(2S)-(5-Bromo-2-piperidin-1-yl-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	600
525	(2S)-(5-Chloro-2-diethylamino-benzoylamino)-3-[3'-(4-methoxy-phenoxy)-biphenyl-4-yl]-propionic acid	573
526	(2S)-(5-Chloro-2-diethylamino-benzoylamino)-3-[3'-(4-trifluoromethoxy-phenoxy)-biphenyl-4-yl]-propionic acid	627
527	3-[3'-(4-tert-Butyl-phenoxy)-biphenyl-4-yl]-(2S)-(5-chloro-2-diethylamino-benzoylamino)-propionic acid	599

EXAMPLE	NAME	LC/MS(m/z)
528	(2S)-(5-Bromo-2-diethylamino-benzoylamino)-3-[3'-(4-trifluoromethyl-phenoxy)-biphenyl-4-yl]-propionic acid	656
529	(2S)-(5-Bromo-2-diethylamino-benzoylamino)-3-[3'-(3-fluoro-phenoxy)-biphenyl-4-yl]-propionic acid	606
530	(2S)-(5-Bromo-2-pyrrolidin-1-yl-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	586
531	(2S)-[5-Chloro-2-(4-methyl-piperazin-1-yl)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	570
532	(2S)-[5-Chloro-2-(4-phenyl-piperazin-1-yl)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	632
533	(2S)-[5-Chloro-2-(3,4-dihydro-1H-isoquinolin-2-yl)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	603
534	(2S)-(5-Chloro-2-morpholin-4-yl-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	557
535	(2S)-(2-Azepan-1-yl-5-chloro-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	569
536	(2S)-[5-Chloro-2-(4-trifluoromethyl-piperidin-1-yl)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	623

## Example 537

(2S)-[5-Chloro-2-(4-methylsulfanyl-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

- 5 A solution of (2S)-(2-amino-5-chloro-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid (0.154 g, 0.307 mmol), prepared by reacting (2S)-amino-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester and 2-amino-5-chlorobenzoic acid by the general procedure A) was reacted with 4-(methylthio)phenylboronic acid (0.130 g, 0.768 mmol),

copper acetate (0.084 g, 0.460 mmol), and triethyl amine (0.215 mL, 1.535 mmol) by the general procedure G. The crude product was purified by flash column chromatography on silica gel using DCM (+25% hexane) to give 0.075 g (39%) of 2-[5-chloro-2-(4-methylsulfanyl-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid methyl ester as a colorless oil. This ester was treated with LiOH (0.019 g, 0.441 mmol) by the general procedure I to give 0.049 g (92%) of 2-[5-chloro-2-(4-methylsulfanyl-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid. LCMS: 610 (M+1)<sup>+</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.94 [bs, 1H], 7.49 [d, 2 H], 7.47 [d, 1 H], 7.22 [m, 10 H], 7.06 [d, 2 H], 6.99 [d, 2 H], 6.88 [d, 2 H], 6.50 [d, 1 H], 4.99 [m, 1 H], 3.30 [m, 2 H], 2.45 [s, 3 H].

#### Example 538

2S-[5-Chloro-2-(3-chloro-4-fluoro-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid

(2S)-(2-amino-5-chloro-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid (0.154 g, 0.307 mmol) prepared above was reacted with 3-Cl, 4-F-phenyl boronic acid (0.13g, 0.77 mmol), copper acetate (0.084 g, 0.460 mmol), and triethyl amine (0.215 mL, 1.535 mmol) as described in the general procedure G. The crude product was purified by column chromatography using DCM as an eluent then hydrolyzed as described in the general procedure I to get the title compound (20 mg, 10%) as a light yellow solid. LCMS: 615(M+1)<sup>+</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 3.12 [m, 1H], 3.39 [m, 1H], 4.84 [m, 1H], 6.61 [m, 1H], 6.79-7.58 [m, 19H], 8.88 [s, 1H].

By analogous methods to those described above the following compounds were synthesized.

EXAMPLE	NAME	LC/MS(m/z)
539	(2S)-[5-Bromo-2-(4-trifluoromethyl-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	676
540	(2S)-(5-Bromo-2-phenylamino-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	608
541	(2S)-(5-Chloro-2-phenylamino-benzoylamino)-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	563
542	(2S)-[5-Chloro-2-(4-trifluoromethyl-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	631

EXAMPLE	NAME	LC/MS(m/z)
543	(2S)-[5-Chloro-2-(3,5-dimethyl-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	591
544	(2S)-[5-Chloro-2-(3-trifluoromethyl-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	631
545	(2S)-[5-Chloro-2-(4-methoxy-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	593
546	(2S)-[2-(4-tert-Butyl-phenylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	619
547	(2S)-[5-Chloro-2-(3,4-difluoro-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	599
548	(2S)-[5-Chloro-2-(4-fluoro-3-methyl-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	595
549	(2S)-[5-Chloro-2-(3,4-dichloro-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	631
550	(2S)-[5-Chloro-2-(4-trifluoromethoxy-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	647
551	(2S)-[5-Chloro-2-(4-methanesulfonyl-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	641
552	(2S)-[2-(4-Benzoyloxy-phenylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	669
553	(2S)-[5-Chloro-2-(naphthalen-1-ylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	613

EXAMPLE	NAME	LC/MS(m/z)
554	(2S)-[5-Chloro-2-(naphthalen-2-ylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	613
555	(2S)-[2-(3,5-Bis-trifluoromethyl-phenylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	699
556	(2S)-[5-Chloro-2-(4-cyclohexyl-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	645
557	(2S)-[2-(Biphenyl-4-ylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	639
558	(2S)-[2-(3-Butoxy-phenylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	635
559	(2S)-[5-Chloro-2-(4-ethoxy-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	607
560	(2S)-[5-Chloro-2-(4-fluoro-3-methoxy-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	611
561	(2S)-[5-Chloro-2-(4-chloro-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	597
562	(2S)-[5-Chloro-2-(3-chloro-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	597
563	(2S)-[5-Chloro-2-(2,4-dichloro-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	631
564	(2S)-[2-(Benzo[1,3]dioxol-5-ylamino)-5-chloro-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	607

EXAMPLE	NAME	LC/MS(m/z)
565	(2S)-[5-Chloro-2-(4-cyano-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	588
566	(2S)-[5-Chloro-2-(4-methoxy-3-methyl-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	607
567	(2S)-[5-Chloro-2-(3-isopropyl-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	605
568	(2S)-[5-Chloro-2-(4-nitro-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	608
569	(2S)-[5-Chloro-2-(4-methyl-3-nitro-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	622

## Example 570

(2S)-{[(2-Biphenyl-4-yl-methoxycarbonyl-ethyl)-(4'-trifluoromethyl-biphenyl-carbonyl)-amino]-methyl}-(2S)-pyrrolidine-1-carboxylic acid tert-butyl ester

5

To a solution of 2-biphenyl-4-yl-(1S)-(methoxycarbonyl)ethylammonium chloride (1.337g, 4.58 mmol) and (2S)-formyl-pyrrolidine-1-carboxylic acid tert-butyl ester (1.0 eq., 913 mg, 4.58 mmol) in a mixture of 25 mL methanol and 25mL THF was added glacial acetic acid (1.5 eq., 0.40mL, 6.87 mmol) and the mixture was stirred at ambient temperature for ten minutes. To this was added a 1.0 N solution of NaCNBH<sub>3</sub> in THF (1.5 eq., 6.87 mL, 6.87 mmol) in small portions and the reaction mixture was stirred at r.t. overnight. The solvent was removed and the residue was dissolved in water and DCM and partitioned. The organic portion was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The crude product was purified by flash column chromatography (2:1 EtOAc;Hexanes, EtOAc) to provide (2S)-[(2-biphenyl-4-yl-(1S)-1-methoxycarbonyl-ethylamino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester (1.440g, 72%) as a clear colorless oil.

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A portion of the product (584mg, 1.33 mmol), dissolved in 13 mL dry CH<sub>2</sub>Cl<sub>2</sub>, was subsequently condensed with 4'-trifluoromethyl-biphenyl-4-carbonyl chloride (1.2 eq, 455 mg, 1.60 mmol) (synthesized from 4'-trifluoromethyl-biphenyl-4-carboxylic acid by heating at reflux in a neat solution of thionyl chloride, followed by removal of excess reagent and

20

volatiles *in vacuo*) in dry CH<sub>2</sub>Cl<sub>2</sub> (13 mL), in the presence of triethylamine (3.0 eq., 3.99 mmol, 0.56 mL) at 0 °C. The reaction was stirred at that temperature and gradually allowed to warm to ambient temperature until the reaction was shown to be complete by TLC. The solvent was removed and the crude residue was purified by flash column chromatography (1:1 EtOAc : hexanes) to afford the title compound, (2S)-{[(2-biphenyl-4-yl-(1S)-methoxycarbonyl-ethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-methyl}-(2S)-pyrrolidine-1-carboxylic acid tert-butyl ester (600 mg, 76%), as a white solid. LCMS 687 (M+1)<sup>+</sup>.

#### Example 571

(2S)-(2-{[(2-Biphenyl-4-yl-1-methoxycarbonyl-ethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-methyl}-(2S)-pyrrolidine-1-sulfonyl)-benzoic acid methyl ester

Into a dry flask was placed 2-(2S)-{[(2-biphenyl-4-yl-(1S)-methoxycarbonyl-ethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester (333 mg, 0.485 mmol) (for preparation, see Example 570), and the flask was capped and purged with dry N<sub>2</sub>. The flask was then charged with 5 mL of 4N HCl/dioxane and stirred at rt for about one hour. The solvent was removed and the crude product was rinsed with ether and dried *in vacuo* to afford 302 mg (100%) of the desired product, (2S)-{[(2biphenyl-4-yl-(1S)-methoxycarbonyl-ethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-methyl}-pyrrolidinium; chloride, which was used without further purification.

The amine hydrochloride (40 mg, 64 micromol) was dissolved in anhydrous acetonitrile (2 mL) and to this was added 2-chlorosulfonyl-benzoic acid methyl ester (3.0 eq., 50 mg, 0.193 mmol), pyridine (0.2 mL) and DMAP (0.1 eq., 0.8mg, 6.4 micromol) and the reaction carried out as described in general procedure F. The crude product was purified by flash column chromatography to afford 40 mg (79%) of the title compound, 2-(2S){[(2-Biphenyl-4-yl-(1S)-methoxycarbonyl-ethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-methyl}-pyrrolidine-1-sulfonyl)-benzoic acid methyl ester. LC/MS 785 (M+1)<sup>+</sup>.

#### Example 572

3-Biphenyl-4-yl-(2S)-{[(2R)-1-(2-thiophen-2-yl-acetyl)-pyrrolidine-2-methyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid

The synthesis of the title compound proceeds through the intermediacy of (2S)-{[(2-biphenyl-4-yl-(1S)-methoxycarbonyl-ethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-methyl}-(2R)-pyrrolidinium chloride, similar in all respects to the intermediate in the synthesis of Example 570, (2S)-{[(2-biphenyl-4-yl-(1S)-methoxycarbonyl-ethyl)-(4' trifluoromethyl-biphenyl-4-carbonyl)-amino]-methyl}-(2S)-pyrrolidinium chloride, in all respects except for the

stereochemical orientation at the 2-position of the pyrrolidine ring. Thus, the synthesis of this intermediate proceeds as described in Examples 570 and 571 with the exception that (2S)-formyl-pyrrolidine-1-carboxylic acid tert-butyl ester is replaced with (2R)-formyl-pyrrolidine-1-carboxylic acid tert-butyl ester in the first step of the sequence.

5 To a solution of (2S)-{[(2-biphenyl-4-yl-(1S)methoxycarbonyl-ethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-methyl}-(2R)-pyrrolidinium chloride (15 mg, 24 micromol) in dry CH<sub>2</sub>Cl<sub>2</sub> under dry N<sub>2</sub> at 0 °C was added 2-thiophene acetyl chloride (3.0 eq., 72 μmol, 8.9 μL) followed by triethylamine (5.0 eq., 0.12 mmol, 17 μL) and the mixture was stirred at 0 °C for one hour, then the solvent was removed. The residue was purified by flash column chromatography (4:1 EtOAc:hexanes) to yield the purified amide, 3-biphenyl-4-yl-(2S)-[1-(2-thiophen-2-yl-acetyl)-pyrrolidin-(2R)-ylmethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester (17 mg, 100%). The ester was saponified according to general procedure C. Thus, 3-biphenyl-4-yl-(2S)-[1-(2-thiophen-2-yl-acetyl)-pyrrolidin-(2R)-ylmethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester (16 mg, 10  
10 23 μmol) was dissolved in 1 mL of a 4:1 mixture of THF and methanol and cooled to 0 °C for the addition of 0.1 mL of 2N aq. LiOH. The reaction furnished the title compound, 3-Biphenyl-4-yl-(2S)-[1-(2-thiophen-2-yl-acetyl)-pyrrolidin-(2R)-ylmethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid (14 mg, 100%) LCMS: 697 (M+1)<sup>+</sup>.

## 20 Example 573

(2S)-[1-(2-(2-Acetylamino-4-methyl-thiazole-5-sulfonylamino)-ethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-3-biphenyl-4-yl-propionic acid methyl ester

To a solution of 2-biphenyl-4-yl-(1S)-methoxycarbonyl-ethyl-ammonium chloride (1.833g, 6.28 mmol) and (2-oxo-ethyl)-carbamic acid tert-butyl ester (1.0 eq., 1.00g, 6.28 mmol), dissolved in a mixture of 25 mL each of THF and methanol, was added glacial acetic acid (2.0 eq., 0.72mL, 12.56 mmol), and after stirring for 10 minutes, NaCNBH<sub>3</sub> in small portions. The reaction mixture was stirred overnight at rt then the volatiles were removed in vacuo. The crude residue was purified by flash column chromatography (3:2 EtOAc:hexanes) to afford the desired secondary amine, 3-Biphenyl-4-yl-(2S)-(2-tert-butoxycarbonylamino-ethylamino)-propionic acid methyl ester (775mg, 31%).

This secondary amine (803 mg, 2.02 mmol) was reacted with 4'-trifluoromethyl-biphenyl-4-carbonyl chloride (1.24 eq., 713mg, 2.50 mmol) (see Example 591 for preparation) in 40 mL anhydrous CH<sub>2</sub>Cl<sub>2</sub> in the presence of triethylamine (3.0 eq., 0.84 mL, 6.06 mmol) at 0 °C for one hour, then the mixture was allowed to warm to ambient temperature and stirred overnight. The volatiles were removed *in vacuo* and the residue was



purified by flash column chromatography (1:1 EtOAc:hexanes) to afford 3-biphenyl-4-yl-(2S)-[[2-tert-butoxycarbonylamino-ethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester (996 mg, 76%). A portion of this compound (395 mg, 0.61 mmol) was placed in a dry flask, capped with a septum and purged with dry N<sub>2</sub>. The flask was charged with 10 mL of 4N HCl / dioxane solution and stirred at r.t. for 1 hour, at which point the reaction was shown to be complete by TLC. The volatiles were removed and the residue was dissolved in ether and triturated with hexanes. The crude product, 2-[(2-biphenyl-4-yl)-(1S)-methoxycarbonyl-ethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-ethyl-ammonium chloride (356 mg, 100%) was used without further purification.

To a mixture of 2-[(2-biphenyl-4-yl-(1S)-methoxycarbonyl-ethyl)-(4'-trifluoro-methyl-biphenyl-4-carbonyl)-amino]-ethyl-ammonium chloride (40 mg, 69  $\mu$ mol) and 2-acetyl-amino-4-methyl-thiazole-5-sulfonyl chloride (3.0 eq., 52.4 mg, 0.21 mmol), in 2 mL anhydrous CH<sub>2</sub>Cl<sub>2</sub> at 0 °C, was added pyridine (5.0 eq., 28  $\mu$ L, 0.34 mmol) and DMAP (0.1 eq., 0.8 mg, 6.9  $\mu$ mol) and the mixture was allowed to gradually warm to ambient temperature and stirred overnight. The solvent was removed and the residue was purified by flash column chromatography (EtOAc) to afford the title compound, (2S)-[[2-(2-Acetylamino-4-methyl-thiazole-5-sulfonylamino)-ethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-3-biphenyl-4-yl-propionic acid methyl ester (42 mg, 80%). LCMS 765 (M+1)<sup>+</sup>.

By analogous methods to those described above the following compounds were synthesized.

EXAMPLE	NAME	LC/MS(m/z)
574	(2S)-[(Biphenyl-4-carbonyl)-(2-hydroxy-benzyl)-amino]-3-biphenyl-4-yl-propionic acid	528
575	(2S)-[(Biphenyl-4-carbonyl)-(4-isopropyl-benzyl)-amino]-3-biphenyl-4-yl-propionic acid	554
576	3-Biphenyl-4-yl-(2S)-[[4-isopropyl-benzyl)-(naphthalene-2-carbonyl)-amino]-propionic acid	528
577	3-Biphenyl-4-yl-(2S)-[[4-tert-butyl-benzoyl)-(4-isopropyl-benzyl)amino]-propionic acid	534

EXAMPLE	NAME	LC/MS(m/z)
578	3-Biphenyl-4-yl-(2S)-[(3,4-dichloro-benzoyl)-(4-isopropyl-benzyl)-amino]-propionic acid	546
579	(2S)-[(Biphenyl-4-carbonyl)-naphthalen-1-ylmethyl-amino]-3-biphenyl-4-yl-propionic acid	562
580	3-Biphenyl-4-yl-(2S)-[(naphthalene-2-carbonyl)-naphthalen-1-ylmethyl-amino]-propionic acid	536
581	3-Biphenyl-4-yl-(2S)-[(4-tert-butyl-benzoyl)-naphthalen-1-ylmethyl-amino]-propionic acid	542
582	3-Biphenyl-4-yl-(2S)-[(3,5-dichloro-benzoyl)-naphthalen-1-ylmethyl-amino]-propionic acid	554
583	3-Biphenyl-4-yl-(2S)-[(naphthalene-1-carbonyl)-naphthalen-1-ylmethyl-amino]-propionic acid	536
584	3-Biphenyl-4-yl-(2S)-[(3,4-dichloro-benzoyl)-naphthalen-1-ylmethyl-amino]-propionic acid	554
585	3-Biphenyl-4-yl-(2S)-[(4-methyl-benzoyl)-naphthalen-1-ylmethyl-amino]-propionic acid	500
586	3-Biphenyl-4-yl-(2S)-[(2,4-dichloro-benzoyl)-naphthalen-1-ylmethyl-amino]-propionic acid	554
587	3-Biphenyl-4-yl-(2S)-[naphthalen-1-yl-methyl-(4-nitro-benzoyl)-amino]-propionic acid	531
588	3-Biphenyl-4-yl-(2S)-[(4-chloro-benzoyl)-naphthalen-1-ylmethyl-amino]-propionic acid	520

EXAMPLE	NAME	LC/MS(m/z)
589	(2S)-[(Biphenyl-4-carbonyl)-(4-chloro-benzyl)-amino]-3-biphenyl-4-yl-propionic acid	546
590	3-Biphenyl-4-yl-(2S)-[(4-chloro-benzyl)-(3,5-dichloro-benzoyl)-amino]-propionic acid	538
591	(2S)-[(Biphenyl-4-carbonyl)-(5-tert-butyl-2-hydroxy-benzyl)-amino]-3-biphenyl-4-yl-propionic acid	584
592	Biphenyl-4-carboxylic acid (2S)-{[(biphenyl-4-carbonyl)-(2-biphenyl-4-yl-1-carboxy-ethyl)-amino]-methyl}-4-tert-butyl-phenyl ester	764
593	3-Biphenyl-4-yl-(2S)-[(4-bromo-benzoyl)-(2-tert-butoxycarbonylamino-ethyl)-amino]-propionic acid	568
594	3-Biphenyl-4-yl-(2S)-[(2-tert-butoxycarbonylamino-ethyl)-(4'-trifluoromethoxy-biphenyl-4-carbonyl)-amino]-propionic acid	649
595	(2S)-[(2-Amino-ethyl)-(4-bromo-benzoyl)-amino]-3-biphenyl-4-yl-propionic acid methyl ester	482
596	(2S)-[(2-Amino-ethyl)-(4-bromo-benzoyl)-amino]-3-biphenyl-4-yl-propionic acid	468
597	3-Biphenyl-4-yl-(2S)-[(4-chloro-benzyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid	614
598	(2S)-{2-[(2-Biphenyl-4-yl-1-carboxy-ethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-ethylsulfamoyl}-benzoic acid	717

EXAMPLE	NAME	LC/MS(m/z)
599	3-Biphenyl-4-yl-(2S)-[[2-(2-methanesulfonyl-benzenesulfonylamino)-ethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid	751
600	(2S)-{[(2-Biphenyl-4-yl-1-methoxycarbonyl-ethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester	687
601	(2S)-{2-[(2-Biphenyl-4-yl-1-methoxycarbonyl-ethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-ethylsulfamoyl}-benzoic acid methyl ester	745
602	3-Biphenyl-4-yl-(2S)-[[2-(2-methanesulfonyl-benzenesulfonylamino)-ethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester	765
603	3-Biphenyl-4-yl-(2S)-[[2-(4-methanesulfonyl-benzenesulfonylamino)-ethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester	765
604	3-Biphenyl-4-yl-(2S)-[[1-(2-methanesulfonyl-benzenesulfonyl)-pyrrolidin-2-ylmethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester	805
605	3-Biphenyl-4-yl-(2S)-[[1-(4-methanesulfonyl-benzenesulfonyl)-pyrrolidin-2-ylmethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester	805

EXAMPLE	NAME	LC/MS(m/z)
606	(2S)-{[(2-Biphenyl-4-yl-1-carboxy-ethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester	673
607	(2S)-{[(2-Biphenyl-4-yl-1-carboxy-ethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester	673
608	(2S)-(2-{[(2-Biphenyl-4-yl-1-carboxy-ethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-methyl}-pyrrolidine-1-sulfonyl)-benzoic acid methylester	771
609	3-Biphenyl-4-yl-(2S)-[[1-(2-methanesulfonyl-benzenesulfonyl)-pyrrolidin-2-ylmethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid	791
610	3-Biphenyl-4-yl-(2S)-[[1-(4-methanesulfonyl-benzenesulfonyl)-pyrrolidin-2-ylmethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid	791
611	(2S)-(2-{[(2-Biphenyl-4-yl-1-methoxycarbonyl-ethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-methyl}-pyrrolidine-1-sulfonyl)-benzoic acid methyl ester	785
612	3-Biphenyl-4-yl-(2S)-[[1-(2-methanesulfonyl-benzenesulfonyl)-pyrrolidin-2-ylmethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester	805

EXAMPLE	NAME	LC/MS(m/z)
613	3-Biphenyl-4-yl-(2S)-[[1-(4-methanesulfonyl-benzenesulfonyl)-pyrrolidin-2-ylmethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester	805
614	3-Biphenyl-4-yl-(2S)-[[1-(2-thiophen-2-yl-acetyl)-pyrrolidin-2-ylmethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester	711
615	(2S)-(2-[[2-Biphenyl-4-yl-1-carboxy-ethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-methyl)-pyrrolidine-1-sulfonyl)-benzoic acid methyl ester	771
616	3-Biphenyl-4-yl-(2S)-[[1-(2-methanesulfonyl-benzenesulfonyl)-pyrrolidin-2-ylmethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid	791
617	3-Biphenyl-4-yl-(2S)-[(1-cyclopentanecarbonyl-pyrrolidin-2-ylmethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester	683
618	3-Biphenyl-4-yl-(2S)-[(1-cyclopropanecarbonyl-pyrrolidin-2-ylmethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester	655
619	3-Biphenyl-4-yl-(2S)-[[1-(4-methanesulfonyl-benzenesulfonyl)-pyrrolidin-2-ylmethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid	791

EXAMPLE	NAME	LC/MS(m/z)
620	(2S)-[(1-Acetyl-pyrrolidin-2-ylmethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-3-biphenyl-4-yl-propionic acid	615
621	3-Biphenyl-4-yl-(2S)-[[1-(2,2-dimethyl-propionyl)-pyrrolidin-2-ylmethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid	657
622	3-Biphenyl-4-yl-(2S)-[(1-cyclopentanecarbonyl-pyrrolidin-2-ylmethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid	669
623	(2S)-[(1-Acetyl-pyrrolidin-2-ylmethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-3-biphenyl-4-yl-propionic acid	615
624	3-Biphenyl-4-yl-(2S)-[(1-cyclopropanecarbonyl-pyrrolidin-2-ylmethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid	641
625	(2S)-[[2-(2-Acetylamino-4-methyl-thiazole-5-sulfonylamino)-ethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-3-biphenyl-4-yl-propionic acid	751
626	3-Biphenyl-4-yl-(2S)-[[2-(5-chloro-1,3-dimethyl-1H-pyrazole-4-sulfonylamino)-ethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid	725
627	3-Biphenyl-4-yl-(2S)-[[2-(3,5-dimethyl-isoxazole-4-sulfonylamino)-ethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid	692
628	3-Biphenyl-4-yl-(2S)-[[2-(1,2-dimethyl-1H-imidazole-4-sulfonylamino)-ethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid	691

EXAMPLE	NAME	LC/MS(m/z)
629	3-Biphenyl-4-yl-(2S)-[[2-(3,5-dimethyl-isoxazole-4-sulfonylamino)-ethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester	706
630	3-Biphenyl-4-yl-(2S)-[[2-(1,2-dimethyl-1H-imidazole-4-sulfonylamino)-ethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester	705
631	3-Biphenyl-4-yl-(2S)-[[2-(5-chloro-1,3-dimethyl-1H-pyrazole-4-sulfonylamino)-ethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester	739
632	3-Biphenyl-4-yl-(2S)-[[2-(1-methyl-1H-imidazole-4-sulfonylamino)-ethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid	677
633	3-Biphenyl-4-yl-(2S)-[[2-(2,4-dimethoxybenzylamino)-ethyl]-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid	683
634	3-Biphenyl-4-yl-(2S)-[[2-(tert-utoxycarbonylamino-ethyl)-(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid	633

## Example 635

2-[[1-(4-Fluoro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino]-3-(4'-trifluoromethoxy-biphenyl-4-yl)-propionic acid

A solution of hydrazine (1.00 mmol), ethyl 2-(ethoxymethylene)-4,4,4-trifluoroacetoacetate (1.00 mmol), and DIEA (1.00 mmol) in anhydrous acetonitrile was stirred at rt for 2 h. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography to give the desired ester as a white solid. This



ester was then hydrolyzed by general procedure J to give the desired 1-(4-Fluoro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carboxylic acid as a white solid.

A solution of above acid in DMF (3.0 mL) was reacted with (2S)-amino-3-(4'-trifluoromethoxy-biphenyl-4-yl)propionic acid methyl ester Hydrochloride (0.300 g, 0.797 mmol), HBTU (0.300 g, 0.797 mmol), and DIEA (0.425 mL, 2.40 mmol) as described in general procedure A. The crude compound was purified by flash column chromatography on silica gel using  $\text{CHCl}_3$  as the mobile phase to give 0.290 g (61%) of 2-[[1-(4-fluoro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino]-3-(4'-trifluoromethoxy-biphenyl-4-yl)-propionic acid methyl ester. A solution of this ester (0.140 g, 0.235 mmol) in THF (4.0 mL) was treated with LiOH (0.035 g) by general procedure I to afford (0.125 g, 92%) of the title compound 2-[[1-(4-Fluoro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino]-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid as a white solid. LCMS: 582 ( $M+1$ )<sup>+</sup>. <sup>1</sup>H NMR ( $\text{DMSO}-d_6$ ) 8.94 [d, 1 H], 8.07 [s, 1 H], 7.76 [m, 2 H], 7.57 [m, 4 H], 7.42 [m, 6 H], 4.64 [m, 1 H], 3.22 [m, 1 H], 3.05 [m, 1 H].

#### Example 636

2-[[1-(4-Fluoro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino]-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid

A solution of 1-(4-Fluoro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carboxylic acid (0.300 g, 1.097 mmol, prepared in example 635) in DMF (4.0 mL) was reacted with (2S)-amino-3-(4'-trifluoromethyl-biphenyl-4-yl)propionic acid methyl ester Hydrochloride (0.394 g, 1.097 mmol), HBTU (0.416 g, 1.097 mmol), and DIEA (0.585 mL, 3.29 mmol) as described in general procedure A. The crude compound was purified by washing with ethyl ether to give 0.300 g (47%) of 2-[[1-(4-Fluoro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino]-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester. A solution of this ester (0.125 g, 0.215 mmol) in THF (4.0 mL) was treated with LiOH (0.031 g) by general procedure I to afford (0.105 g, 87%) the title compound 2-[[1-(4-Fluoro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino]-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid as a white solid. LCMS: 565 ( $M+1$ )<sup>+</sup>. <sup>1</sup>H NMR ( $\text{DMSO}-d_6$ ) 8.92 [d, 1 H], 8.39 [s, 1 H], 8.18 [d, 2 H], 8.09 [d, 2 H], 7.96 [d, 2 H], 7.87 [m, 2 H], 7.71 [m, 4 H], 4.83 [m, 1 H], 3.58 [m, 1 H], 3.36 [m, 1 H].

#### Example 637

(2S)-[[1-(4-Fluoro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino]-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid

A solution of 1-(4-fluoro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carboxylic acid (0.200 g, 0.731 mmol, prepared in example 635) in DMF (4.0 mL) was reacted with 2-L-amino-3-biphenyl-4-yl-propionic acid methyl ester hydrochloride (0.213 g, 0.731 mmol), HBTU (0.277 g, 0.731 mmol), and DIEA (0.450 mL, 2.566 mmol) as described in general procedure A. The crude compound was purified by flash column chromatography on silica gel using CHCl<sub>3</sub> (+10% hexane) to give 0.150 g (41%) of 3-biphenyl-4-yl-2-[[1-(4-fluoro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino]-propionic acid methyl ester. A solution of this ester (0.085 g, 0.166 mmol) in THF (3.0 mL) was treated with LiOH (0.025 g) by general procedure I to afford (0.070 g, 85%) of the title compound 3-Biphenyl-4-yl-2-[[1-(4-fluoro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino]-propionic acid as a white solid. LCMS: 498 (M+1)<sup>+</sup>. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) 8.94 [d, 1 H], 8.08 [s, 1 H], 7.58 [m, 6 H], 7.42 [m, 7 H], 4.63 [m, 1 H], 3.22 [m, 1 H], 3.04 [m, 1 H].

3-Biphenyl-4-yl-(2S)-[[1-(4-fluoro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino]-propionic acid

By analogous methods to those described above the following compounds were synthesized.

EXAMPLE	NAME	LC/MS(m/z)
638	(2S)-[[1-(4-Chloro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino]-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid	582
639	3-Biphenyl-4-yl-(2S)-[[1-(4-chloro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino]-propionic acid	514
640	(2S)-[[1-(4-Chloro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino]-3-(4'-trifluoromethoxy-biphenyl-4-yl)-propionic acid	598
641	2-[[1-(4-Fluoro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino]-3-(6-phenyl-pyridin-3-yl)-propionic acid	499

EXAMPLE	NAME	LC/MS(m/z)
642	(2S)-{[1-(4-Nitro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino}-3-(4'-trifluoromethoxy-biphenyl-4-yl)-propionic acid	609
643	(2S)-{[1-(4-tert-Butyl-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino}-3-(4'-trifluoromethoxy-biphenyl-4-yl)-propionic acid	620
644	(2S)-{[1-(p-Tolyl-5-trifluoromethyl-1H-pyrazole-4-carbonyl)-amino]-3-(4'-trifluoromethoxy-biphenyl-4-yl)-propionic acid	578
645	(2S)-{[1-(6-Methoxy-pyridazin-3-yl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino}-3-(4'-trifluoromethoxy-biphenyl-4-yl)-propionic acid	596
646	(2S)-{[5-Methyl-1-phenyl-1H-pyrazole-4-carbonyl]-amino}-3-(4'-trifluoromethoxy-biphenyl-4-yl)-propionic acid	510
647	(2S)-{[1-(4-Chloro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino}-3-(4'-trifluoromethoxy-biphenyl-4-yl)-propionic acid	598
648	3-(4'-Trifluoromethoxy-biphenyl-4-yl)-(2S)-{[1-(4-trifluoromethoxy-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino}-propionic acid	648
649	(2S)-{[1-(3-Chloro-4-fluoro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-amino}-3-(4'-trifluoromethoxy-biphenyl-4-yl)-propionic acid	616
650	(2S)-{[1-(4-Chloro-phenyl)-1H-pyrazole-4-carbonyl]-amino}-3-(4'-trifluoromethoxy-biphenyl-4-yl)-propionic acid	530

EXAMPLE	NAME	LC/MS(m/z)
651	(2S)-[(1-Phenyl-5-trifluoromethyl-1H-pyrazole-4-carbonyl)-amino]-3-(4'-trifluoromethoxy-biphenyl-4-yl)-propionic acid	564
652	(2S)-[(1-Phenyl-5-trifluoromethyl-1H-pyrazole-4-carbonyl)-amino]-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid	548
653	3-Biphenyl-4-yl-(2S)-[(1-phenyl-5-trifluoromethyl-1H-pyrazole-4-carbonyl)-amino]-propionic acid	480
654	(2S)-[(1-(4-Chloro-phenyl)-5-propyl-1H-pyrazole-4-carbonyl)-amino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid	580

## Example 655

5            3-(Biphenyl-4-ylmethoxy)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid

To a solution of 2-tert-Butoxycarbonylamino-3-hydroxy-propionic acid methyl ester (0.400g, 1.82 mmol) in dimethylformamide (15ml) was added sodium hydride (65%)(0.145g, 3.64 mmol) at 0°C. after the evolution of hydrogen gas ceased, the freshly distilled benzyl  
 10 bromide (0.449 g, 1.82mmol) was added to the solution .The reaction mixture was stirred at 25-30 °C for 5 hr to give a clear solution .The solvent was then removed under reduced pressure below 40°C .The residue was dissolved in water (30ml) and the solution extracted with ethyl acetate(two 20 ml portions).The combined organic layers were further washed with brine and dried over anhydrous sodium sulfate.

15 The ethyl acetate was then removed under reduced pressure to give the 3(biphenyl-4-ylmethoxy)-(2S)-tert-butoxycarbonylamino-propionic acid methyl ester as colorless oil (0.421g, 60%). LC/MS (m/z): 386(M+1).

20 To 3-(Biphenyl-4-ylmethoxy)-(2S)-tert-butoxycarbonylamino-propionic acid methyl ester (0.421 gms, 1.1 mmol) was added 2ml of 4M HCl in dioxane (8.8mmol) and stirred for 30 min. The HCl was then removed under reduced pressure and the residue was then triturated with dichloromethane and hexane for 2-3 times and the solvents were removed

under reduced pressure to yield the HCl salt of the compound (2S)-amino-3- (biphenyl-4-ylmethoxy)-propionic acid methyl ester hydrochloride as a white solid (0.300g, 90%). LC/MS (m/z): 286(M+1).

(2S)-Amino-3- (biphenyl-4-ylmethoxy)-propionic acid methyl ester hydrochloride (0.150g, 0.483mmol) was reacted with 4'-trifluoromethyl-biphenyl-4-carboxylic acid (0.136g, 0.483mmol) as described in general procedure A yielding the 3-(biphenyl-4-ylmethoxy)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester. The resulting compound was then hydrolyzed by following the general procedure C to yield the title compound (0.200g, 80%).

<sup>1</sup>H-NMR(400 MHz, CDCl<sub>3</sub>): 4.2(m, 2H), 4.9 (S, 2H), 5.1 (m, 1H), 7.72(m, 1H), 7.74 (m, 4H), 7.94 (m, 4H), 8.17 (m, 4H), 8.28 (d, 2H), 8.34 (d, 2H), 8.62 (S, 1H), 9.3 (d, 1H); LC/MS (m/z): 520.2 (M+1)<sup>+</sup>.

#### Example 656

3-[(Biphenyl-4-ylmethyl)-amino]-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid.

(2S)-amino-3-tert-butoxycarbonylamino-propionic acid methyl ester hydrochloride (0.200g, 0.785 mmol) was reacted with 4'-trifluoromethyl-biphenyl-4-carboxylic acid (0.208g, 0.785mmol) as described in general procedure A yielding 3-tert-butoxycarbonylamino- (2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester (0.313g, 85%). LC/MS (m/z): 367(M+1).

To 3-tert-butoxycarbonylamino- (2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester (0.313g, 0.671mmol) was added 2ml of 4M HCl in dioxane (3.3mmol) and stirred for 30 min. The HCl was then removed under reduced pressure and the residue was then triturated with dichloromethane and hexane for 2-3 times and the solvents were removed under reduced pressure to yield the HCl salt of the compound 3-amino- (2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester hydrochloride as a white solid (0.300g, 90%). LC/MS (m/z): 267(M+1).

3-Amino- (2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester hydrochloride (0.200g, 0.493 mmol) was subjected to reductive amination as per general procedure E with biphenyl-4-carbaldehyde (0.080g, 0.444mmol) and sodium triacetoxyborohydride (0.208g, 0.986 mmol) to yield the 3-[(biphenyl-4-ylmethyl)-amino]-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester which was further hydrolyzed as per general procedure C to yield 3-[(biphenyl-4-ylmethyl)-amino]-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid (0.190g, 70%).

<sup>1</sup>H-NMR(400 MHz, DMSO-d<sub>6</sub>): 3.9(m, 2H) 4.6(m, 2H), 5.2 (m, 1H), 7.72(m, 1H), 7.78 (m, 2H), 7.98 (m, 4H), 8.05 (bd, 2H), 8.19 (m, 4H), 8.27 (d, 2H), 8.40 (d, 2H), 8.7 (s, 1H), 9.5(d, 1H); LC/MS (m/z): 519.3(M+1).

5      Example 657

3-(Biphenyl-4-ylmethyl-methyl-amino)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid:

10            3-[(Biphenyl-4-ylmethyl)-amino]-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester (0.050g, 0.093mmol) prepared as per the above listed example 656 was subjected to reductive amination as per procedure E with formaldehyde (0.010ml, 0.093mmol) and sodium triacetoxyborohydride (0.039gms, 0.186mmol) to yield the corresponding 3-(Biphenyl-4-ylmethyl-methyl-amino)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester which was then hydrolyzed as per general  
15            procedure C to yield the title compound (0.040g, 80%). <sup>1</sup>H-NMR(400 MHz, DMSO-d<sub>6</sub>): 3.17(s, 3H), 3.9 (m, 2H), 4.76 (m, 2H), 5.31(s, 1H), 7.69(m, 1H), 7.77 (m, 2H), 7.97 (m, 4H), 8.05 (bd, 2H), 8.19 (m, 4H), 8.27 (d, 2H), 8.40 (d, 2H), 9.5(s, 1H); LC/MS (m/z): 533.3(M+1).

20      Example 658

3-(Biphenyl-4-ylmethyl-pyridin-4-ylmethyl-amino)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid:

25            3-[(Biphenyl-4-ylmethyl)-amino]-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester (0.050g, 0.093mmol) prepared as per the above listed example 656 was subjected to reductive amination as per procedure E with 4-pyridine carbaldehyde (0.010ml, 0.093mmol) and sodium triacetoxyborohydride (0.039gms, 0.186mmol) to yield the corresponding 3-(Biphenyl-4-ylmethyl-pyridin-4-yl  
30            methyl-amino)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester which was then hydrolyzed as per general procedure C to yield the title compound (0.040g, 80%). <sup>1</sup>H-NMR(400 MHz, DMSO-d<sub>6</sub>): 3.3 (m, 2H), 4.001 (s, 4H), 5.18(m, 1H), 7.62-7.75 (m, 8H), 7.8-7.93 (m, 4H), 8.17 (m, 4H), 8.27 (m, 4H), 8.77 (d, 2H), 9.1 (d, 1H), 8.7 (s, 1H); LC/MS (m/z): 610.4(M+1).

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Example 659

3-(Biphenyl-4-ylmethyl-furan-2-ylmethyl-amino)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid:

3-[(Biphenyl-4-ylmethyl)-amino]-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester (0.050g, 0.093mmol) prepared as per the above listed example 657 and was subjected to reductive amination as per procedure E with furan-2-carbaldehyde (0.009g, 0.093mmol) and sodium triacetoxyborohydride (0.039gms, 0.186mmol) to yield the corresponding 3-(biphenyl-4-ylmethyl-furan-2-ylmethyl-amino)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester which was then hydrolyzed as per general procedure C to yield the title compound (0.030g, 60%). <sup>1</sup>H-NMR(400 MHz, DMSO-d<sub>6</sub>): 3.21(m, 2H), 4.0 (m, 3H), 6.7(d, 1H), 7.6 (m, 2H), 7.8 (m, 8H), 8.24 (m, 8H); LC/MS (m/z): 599.3(M+1).

#### Example 660

3-[(Biphenyl-4-carbonyl)-amino]-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid:

The 3-amino-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester hydrochloride (0.100g, 0.273mmol) prepared as per the above listed Example 656 was reacted with biphenylcarboxylic acid as per general procedure A to yield the corresponding 3-[(biphenyl-4-carbonyl)-amino]-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester which was then hydrolyzed as per general procedure C to yield the title compound (0.095g, 65%). <sup>1</sup>H-NMR(400 MHz, DMSO-d<sub>6</sub>): 4.16(m, 2H), 4.98 (m, 1H), 7.71(m, 2H), 7.79 (m, 2H), 8.08 (dd, 4H), 8.2-8.4 (m, 9H), 9.16 (m, 1H), 9.2(d, 1H); LC/MS (m/z): 533.2(M+1).

#### Example 661

(2S)-2,3-Bis- [(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]- propionic acid:

(2S)-2,3-Diamino-propionic acid methyl ester (0.080g, 0.421mmol) was reacted with 4'-trifluoromethyl-biphenyl-4-carboxylic acid (0.224g, 0.841mmol) as described in general procedure A yielding the corresponding (2S)-3-bis- [(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester which was then hydrolyzed as per general procedure C to yield the title compound (0.150g, 60%). <sup>1</sup>H-NMR(400 MHz, DMSO-d<sub>6</sub>):

4.16(m, 2H), 5.0 (m, 1H), 8.17(m, 8H), 8.28(m, 8H), 9.18 (m, 1H), 9.21 (d, 1H); LC/MS (m/z): 601.2(M+1).

Example 662

5 3-(Biphenyl-4-sulfonylamino)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid:

To 3-amino-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester hydrochloride (0.100g, 0.273mmol) prepared as per the above listed example  
10 656 was added dry dichloromethane (10 ml) followed by diisopropylethylamine (0.095g, 0.738mmol) and stirred for 10 min. To this mixture at 0°C was added Biphenyl-4-sulfonyl chloride (0.062g, 0.273mmol) and the reaction was stirred at ambient temperature. After 2 hrs the reaction mixture was diluted with dichloromethane and washed with water (20 ml) followed by brine (20 ml). The organic layers were collected and dried over sodium sulfate  
15 and concentrated under reduced pressure to yield the 3-(Biphenyl-4-sulfonylamino)-2-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester which was then hydrolyzed as per procedure C to yield the title compound (0.045g, 50%). <sup>1</sup>H-NMR(400 MHz, DMSO-d<sub>6</sub>): 3.65 (m, 2H), 4.85 (m, 1H), 7.78(m, 4H), 8.02 (d, 2H), 8.17 (m, 7H), 8.27 (m, 4H), 8.62 (s, 1H), 8.9 (bs, 1H). LC/MS  
20 (m/z): 569.1(M+1).

#### Biological Assay

The following assay methods are utilized to identify compounds of Formula (I) that are effective in antagonizing the function of factor IX. Compounds of Formula (I) are effective in antagonizing the function of factor IX and are useful as inhibitors of the intrinsic  
25 clotting pathway.

#### General Assay Procedure

Factor IXa Fluorescence Based Molecular Assay:

Method where a Fluorescent product is generated based on factor IXa cleaving the substrate  
CH<sub>3</sub>SO<sub>2</sub>-(D)-CHG-Gly- Arg-AMC AcOH (methyl sulfonyl-D-cyclohexylglycyl-glycyl-arginine-  
30 7-amino-4-methylcoumarid monoacetate) available from Centerchem, Inc.

12μL of 4X compound dilutions (final 1% DMSO) is incubated for 10 min at room temp with 24 μL FIXa (HCIXA-0050 Haematologic Technologies Inc. Essex Junction, VT) 3.9 units/mL in Buffer containing 80% Ethylene glycol, 10 mM CaCl<sub>2</sub>, 200 mM NaCl, and 100  
35 mM Tris (pH 7.4). The reaction is started by the addition of 12 μL of 0.5 mM FIXa substrate (Pefa-10148 from Pentapharm Basel, Switzerland). After incubating the reaction for 10 min at room temp, the plate is read in a Spectromax Gemini fluorescence plate reader with and



excitation wavelenth of 340 nm and an emmision wavelength of 440 nm. From the varying concentrations of test compound, IC<sub>50</sub>'s are then calculated. The Examples in Table 1 inhibit Factor IX in this assay with IC<sub>50</sub> of less than 30 micromolar.

5 Factor IXa *in vitro* Clotting Assay:

Method where inhibition of clotting using citrated human plasma with exogenous human factor IXa is measured by turbidity.

Potential inhibitors of factor IX are added to a mixture of citrated human plasma, Cephalin, and human factor IX to give a final concentration of 0.8 U/ml. The mixture is  
10 allowed to incubate at 37° C for 10 minutes. Clotting is initiated by the addition of 10 mM CaCl<sub>2</sub>. The optical density is measured at 405 nm for 5 minutes. Relative IC<sub>50</sub>'s as well as maximum efficacy are calculated.

A first control assay is performed using a mixture of citrated human plasma, Cephalin, and human factor IX. A second control assay is performed using a mixture of  
15 citrated human plasma and Cephalin. Clotting for the two control assays is initiated by the addition of CaCl<sub>2</sub>, and the optical density is measured at 405 nm for 5 minutes.

Analysis of graphs of optical denisty versus time for the two control assays and various concentrations of compounds of Formula (I) demonstrates that factor IX decreases the time for Ca<sup>+2</sup> induced clotting of human serum. Analysis also demonstrates that  
20 compounds of Formula (I) prolong the Ca<sup>+2</sup> induced clotting time in the presence of factor IX.

Factor Xa *in vitro* clotting assays were performed using compounds of Formula (I) under the same or similar conditions as the factor IXa *in vitro* clotting assay. These data demonstrate that compounds of Formula (I) are partial inhibitors or partial antagonists of factor IX. For example, where a range of concentrations of a compound of Formula (I) in the  
25 presence of factor IX prolong the Ca<sup>+2</sup> induced clotting time from 700 seconds to 1500 seconds, the same range of concentrations of a compound of Formula (I) in the presence of factor Xa did not alter the Ca<sup>+2</sup> induced clotting time from 200 seconds.

The invention further provides pharmaceutical compositions comprising the factor IX modulating compounds of the invention. The term "pharmaceutical composition" is used  
30 herein to denote a composition that may be administered to a mammalian host, e.g., orally, topically, parenterally, by inhalation spray, or rectally, in unit dosage formulations containing conventional non-toxic carriers, diluents, adjuvants, vehicles and the like. The term "parenteral" as used herein, includes subcutaneous injections, intravenous, intramuscular, intracisternal injection, or by infusion techniques.

35 The term "factor IX" is used herein to refer to blood coagulation factor IX, including both activated and non-activated forms thereof.

The term "therapeutically effective amount" is used herein to denote that amount of a drug or pharmaceutical agent that will elicit the therapeutic response of an animal or human that is being sought.

The pharmaceutical compositions containing a compound of the invention may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous, or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any known method, and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents, and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets may contain the active ingredient in admixture with non-toxic pharmaceutically-acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example corn starch or alginic acid; binding agents, for example, starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in U.S. Patent Nos. 4,356,108; 4,166,452; and 4,265,874, to form osmotic therapeutic tablets for controlled release.

Formulations for oral use may also be presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or a soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions may contain the active compounds in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide such as lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example, heptadecaethyl-eneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more coloring agents, one

or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as a liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active compound in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavoring, and coloring agents may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example, olive oil or arachis oil, or a mineral oil, for example a liquid paraffin, or a mixture thereof. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectible aqueous or oleaginous suspension. This suspension may be formulated according to the known methods using suitable dispersing or wetting agents and suspending agents described above. The sterile injectible preparation may also be a sterile injectible solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conveniently employed as solvent or suspending medium. For this purpose, any bland fixed oil may be employed using synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compositions may also be in the form of suppositories for rectal administration of the compounds of the invention. These compositions can be prepared by mixing the drug

with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will thus melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols, for example.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of the invention are contemplated. For the purpose of this application, topical applications shall include mouth washes and gargles.

The compounds of the present invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes may be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

Also provided by the present invention are prodrugs of the invention.

Pharmaceutically-acceptable salts of the compounds of the present invention, where a basic or acidic group is present in the structure, are also included within the scope of the invention. The term "pharmaceutically acceptable salts" refers to non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid or by reacting the acid with a suitable organic or inorganic base. Representative salts include the following salts: Acetate, Benzenesulfonate, Benzoate, Bicarbonate, Bisulfate, Bitartrate, Borate, Bromide, Calcium Edetate, Camsylate, Carbonate, Chloride, Clavulanate, Citrate, Dihydrochloride, Edetate, Edisylate, Estolate, Esylate, Fumarate, Gluceptate, Gluconate, Glutamate, Glycylglycylsarcosinate, Hexylresorcinate, Hydrabamine, Hydrobromide, Hydrochloride, Hydroxynaphthoate, Iodide, Isethionate, Lactate, Lactobionate, Laurate, Malate, Maleate, Mandelate, Methanesulfonate, Methylbromide, Methylnitrate, Methylsulfate, Monopotassium Maleate, Mucate, Napsylate, Nitrate, N-methylglucamine, Oxalate, Pamotate (Embonate), Palmitate, Pantothenate, Phosphate/diphosphate, Polygalacturonate, Potassium, Salicylate, Sodium, Stearate, Subacetate, Succinate, Tannate, Tartrate, Teoclate, Tosylate, Triethiodide, Trimethylammonium and Valerate. When an acidic substituent is present, such as -COOH, there can be formed the ammonium, morpholinium, sodium, potassium, barium, calcium salt, and the like, for use as the dosage form. When a basic group is present, such as amino or a basic heteroaryl radical, such as pyridyl, an acidic salt, such as hydrochloride, hydrobromide, phosphate, sulfate, trifluoroacetate, trichloroacetate, acetate, oxalate, maleate, pyruvate, malonate, succinate, citrate, tartarate, fumarate, mandelate, benzoate, cinnamate, methanesulfonate, ethanesulfonate, picrate and the like, and include acids related to the pharmaceutically-acceptable salts listed in the Journal of Pharmaceutical Science, 66, 2 (1977) p. 1-19.

Other salts which are not pharmaceutically acceptable may be useful in the preparation of compounds of the invention and these form a further aspect of the invention.

In addition, some of the compounds of Formula (I) may form solvates with water or common organic solvents. Such solvates are also encompassed within the scope of the invention.

Thus, in another aspect of the present invention, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, and one or more pharmaceutically acceptable carriers, excipients, or diluents. In an embodiment of the pharmaceutical composition, the compound of Formula (I) is an antagonist of factor IX activity. In another embodiment of the pharmaceutical composition, the compound of Formula (I) is a partial antagonist of factor IX activity, wherein a partial antagonist comprises a compound that inhibits less than complete activity at a physiologically tolerable dose. In another embodiment of the pharmaceutical composition, the compound of Formula (I) is a partial antagonist of factor IX activity, wherein the compound of Formula (I) inhibits up to 95% of factor IX activity. In another embodiment of the pharmaceutical composition, the compound of Formula (I) is a partial antagonist of factor IX activity, wherein the compound of Formula (I) inhibits up to 80% of factor IX activity. In another embodiment of the pharmaceutical composition, the compound of Formula (I) is a partial antagonist of factor IX activity, wherein the compound of Formula (I) inhibits up to 50% of factor IX activity. In another embodiment of the pharmaceutical composition, the compound of Formula (I) antagonizes blood clotting mediated by factor IX.

In another aspect of the present invention, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, and one or more pharmaceutically acceptable carriers, excipients, or diluents, wherein said therapeutically effective amount of Formula (I) preferentially inhibits the intrinsic clotting cascade as compared to the extrinsic clotting cascade. In an embodiment of the pharmaceutical composition, said therapeutically effective amount of Formula (I) inhibits the intrinsic clotting cascade by greater than 80% and inhibits the extrinsic clotting cascade by less than 50%. In another embodiment of the pharmaceutical composition, said therapeutically effective amount of Formula (I) comprises an amount sufficient to achieve and maintain a sustained blood level that at least partially antagonizes factor IX biological activity. Preferably, said sustained blood level comprises a concentration ranging from about 0.01  $\mu$ M to 2 mM, more preferably from about 1  $\mu$ M to 300  $\mu$ M, and even more preferably from about 20  $\mu$ M to about 100  $\mu$ M.

In another aspect of the present invention, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I), or

a pharmaceutically acceptable salt, solvate, or prodrug thereof, and one or more pharmaceutically acceptable carriers, excipients, or diluents, wherein said therapeutically effective amount comprises a sufficient amount of the compound of Formula (I) to at least partially inhibit the biological activity of factor IX in a subject, a sufficient amount of the compound of Formula (I) for at least partial amelioration of at least one factor IX-mediated disease, or a sufficient amount of the compound of Formula (I) to at least partially inhibit the intrinsic clotting cascade in a subject. In an embodiment of the pharmaceutical composition, said factor IX-mediated disease comprises stroke. In another embodiment of the pharmaceutical composition, said factor IX-mediated disease comprises deep vein thrombosis. In another embodiment of the pharmaceutical composition, said factor IX-mediated disease comprises deep vein thrombosis, wherein said thrombosis is associated with surgical procedures, long periods of confinement, acquired or inherited pro-coagulant states including anti-phospholipid antibody syndrome, protein C deficiency and protein S deficiency, or acute and chronic inflammation including recurrent miscarriage or Systemic Lupus Erythematosis (SLE). In another embodiment, said factor IX-mediated disease comprises excessive clotting associated with the treatment of kidney diseases by hemodialysis and/or venous hemofiltration. In another embodiment, said factor IX-mediated disease comprises cardiovascular disease. In another embodiment, said factor IX-mediated disease comprises cardiovascular disease, wherein said cardiovascular disease comprises myocardial infarction, arrhythmia, or aneurysm.

In another aspect, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of the compound of Formula (I), and one or more pharmaceutically acceptable carriers, excipients, or diluents, wherein said pharmaceutical composition is used to replace or supplement compounds that reduce clotting.

In another aspect, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of the compound of Formula (I), and one or more pharmaceutically acceptable carriers, excipients, or diluents, further comprising one or more therapeutic agents.

In another aspect, the present invention provides a method for the inhibition of the normal biological function of factor IX comprising administering to a subject in need thereof a compound of Formula (I). In embodiment of the method, said compound of Formula (I) is an antagonist of factor IX activity. In another embodiment of the method, said compound of Formula (I) antagonizes blood clotting mediated by factor IX. In another embodiment of the method, said compound of Formula (I) is administered in an amount sufficient to partially antagonize the biological activity of factor IX in said subject. In another embodiment of the method, said compound of Formula (I) is an antagonist of factor IX activity. In another

embodiment of the method, said compound of Formula (I) antagonizes blood clotting mediated by factor IX. In another embodiment of the method, said compound of Formula (I) is administered in an amount sufficient to partially antagonize the biological activity of factor IX in said subject. In another embodiment of the method, said pharmaceutical composition is administered in the form of an oral dosage or parenteral dosage unit. In another embodiment of the method, said compound of Formula (I) is administered as a dose in a range from about 0.01 to 1,000 mg/kg of body weight per day. In another embodiment of the method, said compound of Formula (I) is administered as a dose in a range from about 0.1 to 100 mg/kg of body weight per day. In another embodiment of the method, said compound of Formula (I) is administered as a dose in a range from about 0.5 to 10 mg/kg of body weight per day. In another embodiment, said compound of Formula (I) is used to replace or supplement compounds that reduce clotting.

In another aspect, the present invention provides a method for the inhibition of the normal biological function of factor IX comprising administering to a subject in need thereof a compound of Formula (I), wherein said compound of Formula (I) is administered to said subject as a pharmaceutical composition comprising a therapeutically effective amount of said compound of Formula (I) and one or more pharmaceutically acceptable carriers, excipients, or diluents. In an embodiment of the method, said therapeutically effective amount of the compound of Formula (I) comprises a sufficient amount of the compound of Formula (I) to at least partially inhibit the intrinsic clotting cascade in said subject. In another embodiment of the method, said therapeutically effective amount of Formula (I) preferentially inhibits the intrinsic clotting cascade as compared to the extrinsic clotting cascade. In another embodiment of the method, said therapeutically effective amount of Formula (I) inhibits the intrinsic clotting cascade by greater than 80% and inhibits the extrinsic clotting cascade by less than 50%. In another embodiment of the method, said therapeutically effective amount of the compound of Formula I comprises an amount sufficient to achieve and maintain a sustained blood level that at least partially antagonizes factor IX biological activity. Preferably, said sustained blood level comprises a concentration ranging from about 0.01  $\mu$ M to 2 mM, more preferably from about 1  $\mu$ M to 300  $\mu$ M, and even more preferably from about 20  $\mu$ M to about 100  $\mu$ M. In another embodiment of the method, said pharmaceutical composition further comprises one or more therapeutic agents.

In another aspect, the present invention provides a method for the inhibition of the normal biological function of factor IX comprising administering to a subject in need thereof a compound of Formula (I), wherein said compound of Formula (I) is a partial antagonist of factor IX, wherein a partial antagonist comprises a compound that inhibits less than complete activity at a physiologically tolerable dose. In an embodiment of the method, said compound of Formula (I) inhibits up to 95% of factor IX activity. In another embodiment of

the method, said compound of Formula (I) inhibits up to 80% of factor IX activity. In another embodiment of the method, said compound of Formula (I) inhibits up to 50% of factor IX activity.

In another aspect, the present invention provides a method for the inhibition of the normal biological function of factor IX comprising administering to a subject in need thereof a compound of Formula (I), wherein said compound of Formula (I) is administered to said subject as a pharmaceutical composition comprising a therapeutically effective amount of said compound of Formula (I) and one or more pharmaceutically acceptable carriers, excipients, or diluents, wherein said therapeutically effective amount of the compound of Formula (I) comprises a sufficient amount of the compound of Formula (I) for treatment or prevention of factor IX-mediated diseases. In an embodiment of the method, said factor IX-mediated disease comprises stroke. In another embodiment of the method, said factor IX-mediated disease comprises deep vein thrombosis. The thrombosis may be associated with surgical procedures, long periods of confinement, acquired or inherited pro-coagulant states including anti-phospholipid antibody syndrome, protein C deficiency and protein S deficiency, or acute and chronic inflammation including recurrent miscarriage or Systemic Lupus Erythematosis (SLE). In another embodiment of the method, said factor IX-mediated disease comprises clotting associated with the treatment of kidney disease by hemodialysis and/or venous hemofiltration. In another embodiment of the method, said factor IX-mediated disease comprises cardiovascular disease. The cardiovascular disease may be associated with myocardial infarction, arrhythmia, or aneurysm.

In a further aspect of the present invention, the factor IXa modulators of the invention are utilized in adjuvant therapeutic or combination therapeutic treatments with other known therapeutic agents.

The term "treatment" as used herein, refers to the full spectrum of treatments for a given disorder from which the patient is suffering, including alleviation of one, most of all symptoms resulting from that disorder, to an outright cure for the particular disorder or prevention of the onset of the disorder.

The following is a non-exhaustive listing of adjuvants and additional therapeutic agents which may be utilized in combination with the factor IXa antagonists of the present invention:

1. Analgesics: Aspirin
2. NSAIDs (Nonsteroidal anti-inflammatory drugs): Ibuprofen, Naproxen, Diclofenac
3. DMARDs (Disease-Modifying Antirheumatic drugs): Methotrexate, gold preparations, hydroxychloroquine, sulfasalazine
4. Biologic Response Modifiers, DMARDs: Etanercept, Infliximab  
Glucocorticoids



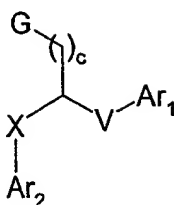
In a further preferred embodiment, the present invention provides a method of treating or preventing a factor IXa mediated diseases, the method comprising administering to a subject in need thereof, a therapeutically effective amount of a compound of Formula (I) alone or in combination with therapeutic agents selected from the group consisting of antibiotics, hormones, biologic response modifiers, analgesics, NSAIDs, DMARDs, glucocorticoids, thrombolytic agents, antidepressants, and anticonvulsants.

Generally speaking, the compound of the present invention, preferably Formula (I), is administered at a dosage level of from about 0.01 to 1000 mg/kg of the body weight of the subject being treated, with a preferred dosage range between 0.01 and 100 mg/kg, most preferably 0.5 to 10 mg/kg of body weight per day. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for oral administration to humans may contain 1 mg to 2 grams of a compound of Formula (I) with an appropriate and convenient amount of carrier material which may vary from about 5 to 95 percent of the total composition. Dosage unit forms will generally contain between from about 5 mg to about 500mg of active ingredient. This dosage has to be individualized by the clinician based on the specific clinical condition of the subject being treated. Thus, it will be understood that the specific dosage level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

While the invention has been described and illustrated with reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the preferred dosages as set forth herein may be applicable as a consequence of variations in the responsiveness of the mammal being treated for factor IXa -mediated disease(s). Likewise, the specific pharmacological responses observed may vary according to and depending on the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention.

We Claim:

1. The compound of Formula (I):



(I)

5

wherein

c is equal to 0, 1, or 2; wherein the values of 0, 1, and 2 comprise a direct bond, -CH<sub>2</sub>-, and -CH<sub>2</sub>-CH<sub>2</sub>-, optionally substituted 1 to 4 times with a substituent group, wherein said substituent group(s) or the term substituted refers to groups comprising: -alkyl, -aryl, -alkylene-aryl, -arylene-alkyl, -alkylene-arylene-alkyl, -O-alkyl, -O-aryl, or -hydroxyl.

10

G comprises: -hydrogen, -CO<sub>2</sub>R<sub>1</sub>, -CH<sub>2</sub>OR<sub>1</sub>, -C(O)-R<sub>1</sub>, -C(R<sub>1</sub>)=N-O-R<sub>2</sub>, or an acid isostere; wherein R<sub>1</sub> and R<sub>2</sub> independently comprise: -hydrogen, -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, or -alkylene-arylene-alkyl.

15

V comprises: -(CH<sub>2</sub>)<sub>b</sub>-O-(CH<sub>2</sub>)<sub>a</sub>-, -(CH<sub>2</sub>)<sub>b</sub>-N(R<sub>7</sub>)-(CH<sub>2</sub>)<sub>a</sub>-, -(CH<sub>2</sub>)<sub>b</sub>-O-, -(CH<sub>2</sub>)<sub>b</sub>-N(R<sub>7</sub>), -(CH<sub>2</sub>)<sub>a</sub>-, or a direct bond; in which a is equal to 0, 1, or 2, b is equal to 1 or 2, and R<sub>7</sub> comprises: -hydrogen, -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, or -alkylene-arylene-alkyl;

wherein

20

the alkylene groups of V are optionally substituted 1 to 4 times with a substituent group, wherein said substituent group(s) or the term substituted refers to groups comprising: -alkyl, -aryl, -alkylene-aryl, -arylene-alkyl, -alkylene-arylene-alkyl, -O-alkyl, -O-aryl, or -hydroxyl.

25

X comprises: -N(R<sub>8</sub>)-, -CON(R<sub>8</sub>)-, -N(R<sub>8</sub>)CO-, -N(R<sub>8</sub>)CON(R<sub>9</sub>)-, -OC(O)N(R<sub>8</sub>)-, -SO<sub>2</sub>N(R<sub>8</sub>)-, or -N(R<sub>8</sub>)SO<sub>2</sub>N(R<sub>9</sub>)-;

wherein

30

R<sub>8</sub> and R<sub>9</sub> independently comprise: -hydrogen, -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, -alkylene-arylene-alkyl, -alkylene-cycloalkylene-C(O)-alkylene-aryl, -alkylene-heterocyclylene-C(O)-alkylene-aryl, -alkylene-C(H)(R<sub>10</sub>)(R<sub>11</sub>), or -alkylene-N-(R<sub>10</sub>)(R<sub>11</sub>),

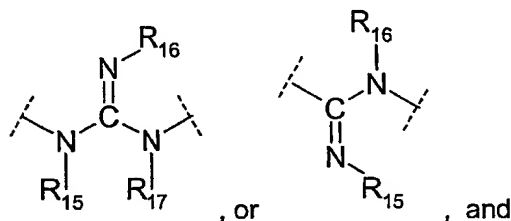
wherein

- $R_{10}$  comprises H, alkyl, alkylene-aryl, alkylene-heteroaryl, aryl, or heteroaryl, and
- $R_{11}$  comprises H, -alkyl, -alkylene-aryl, -alkylene-heteroaryl, -aryl, -heteroaryl, -C(O)-O-alkyl, -C(O)-O-alkylene-aryl, -C(O)-O-alkylene-heteroaryl, -C(O)-alkyl, -C(O)-alkylene-aryl, -C(O)-alkylene-heteroaryl, -S(O)<sub>2</sub>-alkyl, -S(O)<sub>2</sub>-aryl, -S(O)<sub>2</sub>-heteroaryl, -S(O)<sub>2</sub>-alkylene-aryl, -S(O)<sub>2</sub>-alkylene-heteroaryl, -S(O)<sub>2</sub>-NH-alkyl, -S(O)<sub>2</sub>-NH-alkylene-aryl, -S(O)<sub>2</sub>-NH-alkylene-heteroaryl, -S(O)<sub>2</sub>-NH-aryl, or -S(O)<sub>2</sub>-NH-heteroaryl;
- $R_{10}$  and  $R_{11}$  may be taken together to form a ring having the formula  $-(CH_2)_m-Z-(CH_2)_n-$  bonded to the nitrogen or carbon atom to which  $R_{10}$  and  $R_{11}$  are attached, wherein m and n are, independently, 1, 2, 3, or 4; Z independently comprises -CH<sub>2</sub>-, -C(O)-, -O-, -N(H)-, -S-, -S(O)-, -S(O<sub>2</sub>)-, -CON(H)-, -NHC(O)-, -NHC(O)N(H)-, -NH(SO<sub>2</sub>)-, -S(O<sub>2</sub>)N(H)-, -(O)CO-, -NHS(O<sub>2</sub>)NH-, -OC(O)-, -N(R<sub>12</sub>)-, -N(C(O)R<sub>12</sub>)-, -N(C(O)NHR<sub>12</sub>)-, -N(S(O<sub>2</sub>)NHR<sub>12</sub>)-, -N(SO<sub>2</sub>R<sub>12</sub>)-, or -N(C(O)OR<sub>12</sub>)-; wherein R<sub>12</sub> comprises hydrogen, aryl, alkyl, or alkylene-aryl; or
- $R_{10}$  and  $R_{11}$  may be taken together, with the nitrogen or carbon atom to which they are attached, to form a heterocyclyl or heteroaryl ring.
- Ar<sub>1</sub> comprises an aryl, heteroaryl, fused cycloalkylaryl, fused cycloalkylheteroaryl, fused heterocyclylaryl, or fused heterocyclylheteroaryl group optionally substituted 1 to 7 times, wherein the substituents independently comprise:
- a) -fluoro;
  - b) -chloro;
  - c) -bromo;
  - d) -iodo;
  - e) -cyano;
  - f) -nitro;
  - g) -perfluoroalkyl;
  - h) -D<sub>1</sub>-R<sub>13</sub>;
  - i) -alkyl;
  - j) -aryl;
  - k) -heteroaryl;
  - l) -heterocyclyl;
  - m) -cycloalkyl;
  - n) -alkylene-aryl;
  - o) -alkylene-heteroaryl;

- 5 p) -alkylene-arylene-D<sub>1</sub>-R<sub>13</sub>;  
 q) -alkylene-heteroarylene-D<sub>1</sub>-R<sub>13</sub>;  
 r) -alkylene-arylene-aryl;  
 s) -alkylene-heteroarylene-aryl;  
 t) -alkylene-arylene-heteroaryl  
 u) -alkylene-arylene-arylene-D<sub>1</sub>-R<sub>13</sub>;  
 v) -alkylene-arylene-alkyl;  
 w) -alkylene-heteroarylene-alkyl;  
 10 x) -arylene-alkyl;  
 y) -arylene-cycloalkyl;  
 z) -heteroarylene-alkyl;  
 aa) -arylene-arylene-alkyl;  
 bb) - D<sub>1</sub>-alkyl;  
 cc) - D<sub>1</sub>-aryl;  
 15 dd) - D<sub>1</sub>-heteroaryl;  
 ee) -D<sub>1</sub>-arylene-D<sub>2</sub>-R<sub>14</sub>;  
 ff) -D<sub>1</sub>-heteroarylene-D<sub>2</sub>-R<sub>14</sub>;  
 gg) - D<sub>1</sub>-alkylene-heteroaryl;  
 hh) - D<sub>1</sub>-alkylene-aryl;  
 20 ii) -D<sub>1</sub>-alkylene-arylene-D<sub>2</sub>-R<sub>14</sub>  
 jj) -D<sub>1</sub>-alkylene-heteroarylene-D<sub>2</sub>-R<sub>14</sub>  
 kk) - D<sub>1</sub>-arylene-alkyl;  
 ll) - D<sub>1</sub>-heteroarylene-alkyl;  
 mm) - D<sub>1</sub>-alkylene-arylene-aryl;  
 25 nn) - D<sub>1</sub>-alkylene-heteroarylene-aryl;  
 oo) - D<sub>1</sub>-arylene-arylene-aryl;  
 pp) - D<sub>1</sub>-alkylene-arylene-alkyl;  
 qq) - D<sub>1</sub>-alkylene-heteroarylene-alky  
 ss) -alkylene-D<sub>1</sub>-alkylene-aryl;  
 30 tt) -alkylene-D<sub>1</sub>-alkylene-arylene-D<sub>2</sub>-R<sub>14</sub>  
 uu) -arylene- D<sub>1</sub>-alkyl;  
 vv) -arylene- D<sub>1</sub>-cycloalkyl;  
 ww) -arylene- D<sub>1</sub>-heterocyclyl;  
 xx) -alkylene- D<sub>1</sub>-aryl;  
 35 yy) -alkylene- D<sub>1</sub>-heteroaryl;  
 zz) -alkylene-D<sub>1</sub>-arylene-D<sub>2</sub>-R<sub>14</sub>  
 aaa) -alkylene-D<sub>1</sub>-heteroarylene-D<sub>2</sub>-R<sub>14</sub>

- bbb) -alkylene- D<sub>1</sub>-heteroaryl;  
 ccc) -alkylene- D<sub>1</sub>-cycloalkyl;  
 ddd) -alkylene- D<sub>1</sub>-heterocyclyl;  
 eee) -alkylene- D<sub>1</sub>-arylene-alkyl;  
 5    fff) -alkylene- D<sub>1</sub>-heteroarylene-alkyl;  
 ggg) -alkylene- D<sub>1</sub>-alkylene-arylene-alkyl;  
 hh) -alkylene- D<sub>1</sub>-alkylene-heteroarylene-alkyl;  
 iii) -alkylene- D<sub>1</sub>-alkyl;  
 jjj) -alkylene- D<sub>1</sub>-R<sub>13</sub>;  
 10    kkk) -arylene- D<sub>1</sub>-R<sub>13</sub>;  
 lll) -heteroarylene-D<sub>1</sub>-R<sub>13</sub>; or  
 mmm) -hydrogen;  
 wherein

D<sub>1</sub> comprises -CH<sub>2</sub>-, -alkylene-, -alkenylene-, -alkylene-S-, -S-alkylene-, -  
 15    alkylene-O-, -O-alkylene-, -alkylene-S(O)<sub>2</sub>-, -S(O)<sub>2</sub>-alkylene, -O-, -N(R<sub>15</sub>)-, -  
 C(O)-, -CON(R<sub>15</sub>)-, -N(R<sub>15</sub>)C(O)-, -N(R<sub>15</sub>)CON(R<sub>16</sub>)-, -N(R<sub>15</sub>)C(O)O-,  
 -OC(O)N(R<sub>15</sub>)-, -N(R<sub>15</sub>)SO<sub>2</sub>-, -SO<sub>2</sub>N(R<sub>15</sub>)-, -C(O)-O-, -O-C(O)-, -S-, -S(O)-, -  
 S(O<sub>2</sub>)-, -N(R<sub>15</sub>)SO<sub>2</sub>N(R<sub>16</sub>)-,



20    wherein R<sub>13</sub>, R<sub>15</sub>, R<sub>16</sub>, and R<sub>17</sub> independently comprise: -hydrogen, -alkyl, -  
 aryl, -heteroaryl, -arylene-alkyl, -heteroarylene-alkyl, -alkylene-aryl, -  
 alkylene-heteroaryl, -alkylene-arylene-alkyl, or -alkylene-heteroarylene-  
 alkyl;

D<sub>2</sub> comprises -CH<sub>2</sub>-, -alkylene-, -alkenylene-, -alkylene-S-, -S-alkylene-, -  
 25    alkylene-O-, -O-alkylene-, -alkylene-S(O)<sub>2</sub>-, -S(O)<sub>2</sub>-alkylene, -O-, -N(R<sub>25</sub>)-, -  
 C(O)-, -CON(R<sub>25</sub>)-, -N(R<sub>18</sub>)C(O)-, -N(R<sub>18</sub>)CON(R<sub>19</sub>)-, -N(R<sub>18</sub>)C(O)O-,  
 -OC(O)N(R<sub>18</sub>)-, -N(R<sub>18</sub>)SO<sub>2</sub>-, -SO<sub>2</sub>N(R<sub>18</sub>)-, -C(O)-O-, -O-C(O)-, -S-, -S(O)-, -  
 S(O<sub>2</sub>)-, -N(R<sub>18</sub>)SO<sub>2</sub>N(R<sub>19</sub>)-, and

30    wherein R<sub>18</sub> and R<sub>19</sub> independently comprise: -hydrogen, -alkyl, -aryl, -  
 arylene-alkyl, -alkylene-aryl, or -alkylene-arylene-alkyl; and

R<sub>14</sub> comprises -hydrogen, -alkyl, -aryl, -heteroaryl, -arylene-alkyl, -heteroarylene-  
 alkyl, -alkylene-aryl, -alkylene-heteroaryl, -alkylene-arylene-alkyl, or -alkylene-  
 heteroarylene-alkyl;

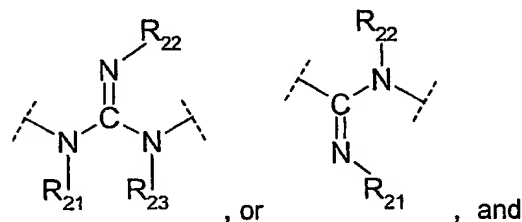
Ar<sub>2</sub> comprises an aryl or heteroaryl group optionally substituted 1 to 7 times, wherein the substituents independently comprise:

- |    |     |  |
|----|-----|--|
|    | a)  | -fluoro;                                     |
| 5  | b)  | -chloro;                                     |
|    | c)  | -bromo;                                      |
|    | d)  | -iodo;                                       |
|    | e)  | -cyano;                                      |
|    | f)  | -nitro;                                      |
| 10 | g)  | -perfluoroalkyl;                             |
|    | h)  | -T <sub>1</sub> -R <sub>20</sub> ;           |
|    | i)  | -alkyl;                                      |
|    | j)  | -aryl;                                       |
|    | k)  | -heteroaryl;                                 |
| 15 | l)  | -heterocyclyl;                               |
|    | m)  | -cycloalkyl;                                 |
|    | n)  | -alkylene-aryl;                              |
|    | o)  | -alkylene-arylene-aryl;                      |
|    | p)  | -alkylene-arylene-alkyl;                     |
| 20 | q)  | -arylene-alkyl;                              |
|    | r)  | -arylene-aryl;                               |
|    | s)  | -arylene-heteroaryl;                         |
|    | t)  | -heteroarylene-aryl;                         |
|    | u)  | -heteroarylene-heteroaryl;                   |
| 25 | v)  | -heteroarylene-heterocyclyl                  |
|    | w)  | -arylene-heterocyclyl                        |
|    | x)  | -arylene-arylene-alkyl;                      |
|    | y)  | - T <sub>1</sub> -alkyl;                     |
|    | z)  | - T <sub>1</sub> -aryl;                      |
| 30 | aa) | - T <sub>1</sub> -alkylene-aryl;             |
|    | bb) | - T <sub>1</sub> -alkenylene-aryl;           |
|    | cc) | - T <sub>1</sub> -alkylene-heteroaryl;       |
|    | dd) | - T <sub>1</sub> -alkenylene-heteroaryl;     |
|    | ee) | - T <sub>1</sub> -cycloalkylene-aryl;        |
| 35 | ff) | - T <sub>1</sub> -cycloalkylene-heteroaryl;  |
|    | gg) | -T <sub>1</sub> -heterocyclylene-aryl;       |
|    | hh) | -T <sub>1</sub> -heterocyclylene-heteroaryl; |

- ii) - T<sub>1</sub>-arylene-alkyl;  
 jj) - T<sub>1</sub>-arylene-alkenyl;  
 kk) - T<sub>1</sub>-alkylene-arylene-aryl;  
 ll) - T<sub>1</sub>-arylene-T<sub>2</sub>-aryl;  
 5 mm) - T<sub>1</sub>-arylene-arylene-aryl;  
 nn) - T<sub>1</sub>-alkylene-arylene-alkyl;  
 oo) -alkylene-T<sub>1</sub>-alkylene-aryl;  
 pp) -arylene-T<sub>1</sub>-alkyl;  
 qq) -arylene-T<sub>1</sub>-alkylene-aryl;  
 10 rr) -T<sub>1</sub>-alkylene-T<sub>2</sub>-aryl;  
 ss) -T<sub>1</sub>-alkylene-aryl;  
 tt) -alkylene-T<sub>1</sub>-heteroaryl;  
 uu) -alkylene-T<sub>1</sub>-cycloalkyl;  
 vv) -alkylene-T<sub>1</sub>-heterocyclyl;  
 15 ww) -alkylene-T-arylene-alkyl;  
 xx) -alkylene-T<sub>1</sub>-alkylene-arylene-alkyl;  
 yy) -alkylene-T<sub>1</sub>-alkyl;  
 zz) -alkylene-T<sub>1</sub>-R<sub>20</sub>;  
 aaa) -arylene-T<sub>1</sub>-R<sub>20</sub>; or  
 20 bbb) -hydrogen;

wherein

T<sub>1</sub> comprises -CH<sub>2</sub>-, -O-, -N(R<sub>21</sub>)-, -C(O)-, -CON(R<sub>21</sub>)-, -N(R<sub>21</sub>)C(O)-,  
 -N(R<sub>21</sub>)CON(R<sub>22</sub>)-, -N(R<sub>21</sub>)C(O)O-, -OC(O)N(R<sub>21</sub>)-, -N(R<sub>21</sub>)SO<sub>2</sub>-, -SO<sub>2</sub>N(R<sub>21</sub>)-,  
 -C(O)-O-, -O-C(O)-, -S-, -S(O)-, -S(O<sub>2</sub>)-, -N(R<sub>21</sub>)SO<sub>2</sub>N(R<sub>22</sub>)-,



wherein R<sub>20</sub>, R<sub>21</sub>, R<sub>22</sub> and R<sub>23</sub>, independently comprise: -hydrogen, -alkyl, -  
 alkenyl, -alkylene-cycloalkyl, -alkynene-heterocyclyl, -aryl, -heteroaryl, -  
 arylene-alkyl, -alkylene-aryl, -alkylene-arylene-alkyl, -alkylene-arylene-  
 aryl, -alkylene-arylene-alkylene-aryl, -alkylene-arylene-O-arylene, or  
 30 alkylene-arylene-O-alkylene-aryl; and

T<sub>2</sub> comprises a direct bond, -CH<sub>2</sub>-, -O-, -N(R<sub>24</sub>)-, -C(O)-, -CON(R<sub>24</sub>)-,  
 -N(R<sub>24</sub>)C(O)-, -N(R<sub>24</sub>)CON(R<sub>25</sub>)-, -N(R<sub>24</sub>)C(O)O-, -OC(O)N(R<sub>24</sub>)-, -N(R<sub>24</sub>)SO<sub>2</sub>-,  
 -SO<sub>2</sub>N(R<sub>24</sub>)-, -C(O)-O-, -O-C(O)-, -S-, -S(O)-, -S(O<sub>2</sub>)-, -N(R<sub>24</sub>)SO<sub>2</sub>N(R<sub>25</sub>)-,  
 wherein R<sub>24</sub> and R<sub>25</sub> independently comprise; -hydrogen, -alkyl, -alkenyl,  
 5 -alkylene-cycloalkyl, alkynene-heterocyclyl, -aryl, -heteroaryl, -arylene-  
 alkyl, -alkylene-aryl, and -alkylene-arylene-alkyl.

and wherein

the alkyl, aryl, heteroaryl, alkylene, and arylene groups in Ar<sub>1</sub>, Ar<sub>2</sub>, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>,  
 R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub>, R<sub>11</sub>, R<sub>12</sub>, R<sub>13</sub>, R<sub>14</sub>, R<sub>15</sub>, R<sub>16</sub>, R<sub>17</sub>, R<sub>18</sub>, R<sub>19</sub>, R<sub>20</sub>, R<sub>21</sub>, R<sub>22</sub>, and R<sub>23</sub>  
 10 may be optionally substituted 1 to 4 times with a substituent group, wherein said  
 substituent group(s) or the term substituted refers to groups comprising:

- a) -hydrogen;
- b) -fluoro;
- c) -chloro;
- 15 d) -bromo;
- e) -iodo;
- f) -cyano;
- g) -nitro;
- h) <sup>l</sup> -perfluoroalkyl;
- 20 i) -Q-perfluoroalkyl
- j) -Q-R<sub>24</sub>;
- k) -Q-alkyl;
- l) -Q-aryl;
- m) -Q-alkylene-aryl;
- 25 n) -Q-alkylene-NR<sub>25</sub>R<sub>26</sub>; or
- o) -Q-alkyl-W-R<sub>27</sub>;

wherein

Q and W independently comprise: -CH<sub>2</sub>-, -O-, -N(R<sub>28</sub>)-, -C(O)-,  
 -CON(R<sub>28</sub>)-, -N(R<sub>28</sub>)C(O)-, -N(R<sub>28</sub>)CON(R<sub>29</sub>)-, -N(R<sub>28</sub>)C(O)O-,  
 30 -OC(O)N(R<sub>28</sub>)-, -N(R<sub>28</sub>)SO<sub>2</sub>-, -SO<sub>2</sub>N(R<sub>28</sub>)-, -C(O)-O-, -O-C(O)-, or  
 -N(R<sub>28</sub>)SO<sub>2</sub>N(R<sub>29</sub>)-,

wherein

R<sub>24</sub>, R<sub>25</sub>, R<sub>26</sub>, R<sub>27</sub>, R<sub>28</sub>, and R<sub>29</sub> independently comprise: -hydrogen,  
 -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, or -alkylene-arylene-  
 35 alkyl.



29. The compound of Formula (I) in claim 1,  
wherein

c is equal to 0;

G comprises: -hydrogen or  $-\text{CO}_2\text{H}$ ;

5 V comprises:  $-\text{CH}_2-$  or a direct bond;

X comprises:  $-\text{CON}(\text{R}_8)-$ , or  $-\text{N}(\text{R}_8)\text{CO}-$ ;

wherein  $\text{R}_8$  comprises: -hydrogen;

$\text{Ar}_1$  comprises a mono-substituted phenyl group wherein the substituent comprises: -aryl,  
-arylene-alkyl,  $-\text{D}_1$ -aryl,  $-\text{D}_1$ -alkylene-arylene-alkyl, or -arylene- $\text{D}_1$ -alkyl,

10 wherein

$\text{D}_1$  comprises  $-\text{O}-$ , or  $-\text{N}(\text{R}_{15})-$ ,

wherein

$\text{R}_{15}$  comprises: -hydrogen, -alkyl, or -aryl; and

$\text{Ar}_2$  comprises a substituted phenyl, 2-naphthyl, 2-pyridyl, 3-isoquinolyl, 2-pyrimidyl or 2-  
15 quinazolyl group having 1 to 5 substituents independently comprising: -hydrogen, -  
fluoro, -chloro, -bromo, iodo, -cyano, -nitro, -perfluoroalkyl,  $-\text{T}_1$ - $\text{R}_{14}$ , -alkyl, -aryl, -  
arylene-alkyl,  $-\text{T}_1$ -alkyl,  $-\text{T}_1$ -alkylene-aryl,  $-\text{T}_1$ -alkylene-arylene-aryl,  $-\text{T}_1$ -alkylene-  
arylene-alkyl, or -arylene- $\text{T}_1$ -alkyl;

wherein

20  $\text{T}_1$  comprises  $-\text{CH}_2-$ ,  $-\text{O}-$ ,  $-\text{N}(\text{R}_{21})-$ ,  $-\text{CON}(\text{R}_{21})-$ , or  $-\text{N}(\text{R}_{21})\text{C}(\text{O})-$ ;

wherein

$\text{R}_{21}$  comprises: -hydrogen, -alkyl, or -aryl,

wherein the alkyl, aryl, alkylene, and arylene groups in  $\text{Ar}_1$  and  $\text{Ar}_2$  may be optionally  
substituted 1 to 4 times with a substituent group, wherein said substituent group(s) or  
25 the term substituted refers to groups comprising: -hydrogen, -fluoro, -chloro, -bromo,  
iodo, -cyano, -nitro, or -perfluoroalkyl.

2. The compound of Formula (I) in claim 1, wherein c is equal to 0 or 1.

30 3. The compound of Formula (I) in claim 1, wherein c is equal to 0.

4. The compound of Formula (I) in claim 1, wherein G comprises: -hydrogen or  
 $-\text{CO}_2\text{R}_1$ ; wherein  $\text{R}_1$  comprises: -hydrogen, -alkyl, and -aryl.

35 5. The compound of Formula (I) in claim 1, wherein c is equal to 0 and G comprises:  
-hydrogen or  $-\text{CO}_2\text{H}$ .

6. The compound of Formula (I) in claim 1, wherein V comprises  $-(CH_2)_a-$ ,  $-(CH_2)_b-$ ,  $O-(CH_2)_a-$ , or a direct bond, wherein a is equal to 1 or 2 and b is equal to 1.

7. The compound of Formula (I) in claim 1, wherein V comprises  $-(CH_2)_a-$  or a direct bond, wherein a is equal to 1.

8. The compound of Formula (I) in claim 1, wherein X comprises  $-N(R_8)-$ ,  $-CON(R_8)-$ ,  $-N(R_8)CO-$ , or  $-N(R_8)CON(R_9)-$ ,

wherein

10  $R_8$  and  $R_9$  independently comprise: -hydrogen, -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, or -alkylene-arylene-alkyl.

9. The compound of Formula (I) in claim 1, wherein X comprises  $-N(R_8)-$ ,  $-CON(R_8)-$ , or  $-N(R_8)CO-$ ,

15 wherein

$R_8$  comprises: -hydrogen, -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, or -alkylene-arylene-alkyl.

10. The compound of Formula (I) in claim 1, wherein  $Ar_1$  comprises a mono- or bicyclic aryl or heteroaryl group optionally substituted 1 to 7 times.

11. The compound of Formula (I) in claim 1, wherein  $Ar_1$  comprises a phenyl group having 1 to 5 substituents, wherein the substituents independently comprise:

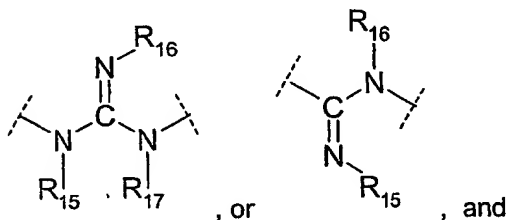
- a) -fluoro;
- 25 b) -chloro;
- c) -bromo;
- d) -iodo;
- e) -cyano;
- f) -nitro;
- 30 g) -perfluoroalkyl;
- h)  $-D_1-R_{13}$ ;
- i) -alkyl;
- j) -aryl;
- k) -heteroaryl;
- 35 l) -heterocyclyl;
- m) -cycloalkyl;
- n) -alkylene-aryl;

- o) -alkylene-heteroaryl;
- p) -alkylene-arylene-D<sub>1</sub>-R<sub>13</sub>;
- q) -alkylene-heteroarylene-D<sub>1</sub>-R<sub>13</sub>;
- r) -alkylene-arylene-aryl;
- 5 s) -alkylene-heteroarylene-aryl;
- t) -alkylene-arylene-heteroaryl
- u) -alkylene-arylene-arylene-D<sub>1</sub>-R<sub>13</sub>;
- v) -alkylene-arylene-alkyl;
- w) -alkylene-heteroarylene-alkyl;
- 10 x) -arylene-alkyl;
- y) -arylene-cycloalkyl;
- z) -heteroarylene-alkyl;
- aa) -arylene-arylene-alkyl;
- bb) - D<sub>1</sub>-alkyl;
- 15 cc) - D<sub>1</sub>-aryl;
- dd) - D<sub>1</sub>-heteroaryl;
- ee) -D<sub>1</sub>-arylene-D<sub>2</sub>-R<sub>14</sub>;
- ff) -D<sub>1</sub>-heteroarylene-D<sub>2</sub>-R<sub>14</sub>;
- gg) - D<sub>1</sub>-alkylene-heteroaryl;
- 20 hh) - D<sub>1</sub>-alkylene-aryl;
- ii) -D<sub>1</sub>-alkylene-arylene-D<sub>2</sub>-R<sub>14</sub>
- jj) -D<sub>1</sub>-alkylene-heteroarylene-D<sub>2</sub>-R<sub>14</sub>
- kk) - D<sub>1</sub>-arylene-alkyl;
- ll) - D<sub>1</sub>-heteroarylene-alkyl;
- 25 mm) - D<sub>1</sub>-alkylene-arylene-aryl;
- nn) - D<sub>1</sub>-alkylene-heteroarylene-aryl;
- oo) - D<sub>1</sub>-arylene-arylene-aryl;
- pp) - D<sub>1</sub>-alkylene-arylene-alkyl;
- qq) - D<sub>1</sub>-alkylene-heteroarylene-alky
- 30 ss) -alkylene-D<sub>1</sub>-alkylene-aryl;
- tt) -alkylene-D<sub>1</sub>-alkylene-arylene-D<sub>2</sub>-R<sub>14</sub>
- uu) -arylene- D<sub>1</sub>-alkyl;
- vv) -arylene- D<sub>1</sub>-cycloalkyl;
- ww) -arylene- D<sub>1</sub>-heterocyclyl;
- 35 xx) -alkylene- D<sub>1</sub>-aryl;
- yy) -alkylene- D<sub>1</sub>-heteroaryl;
- zz) -alkylene-D<sub>1</sub>-arylene-D<sub>2</sub>-R<sub>14</sub>

- aaa) -alkylene-D<sub>1</sub>-heteroarylene-D<sub>2</sub>-R<sub>14</sub>  
 bbb) -alkylene- D<sub>1</sub>-heteroaryl;  
 ccc) -alkylene- D<sub>1</sub>-cycloalkyl;  
 ddd) -alkylene- D<sub>1</sub>-heterocyclyl;  
 5 eee) -alkylene- D<sub>1</sub>-arylene-alkyl;  
 fff) -alkylene- D<sub>1</sub>-heteroarylene-alkyl;  
 ggg) -alkylene- D<sub>1</sub>-alkylene-arylene-alkyl;  
 hh) -alkylene- D<sub>1</sub>-alkylene-heteroarylene-alkyl;  
 iii) -alkylene- D<sub>1</sub>-alkyl;  
 10 jjj) -alkylene- D<sub>1</sub>-R<sub>13</sub>;  
 kkk) -arylene- D<sub>1</sub>-R<sub>13</sub>;  
 lll) -heteroarylene-D<sub>1</sub>-R<sub>13</sub>; or  
 mmm) -hydrogen;

wherein

15 D<sub>1</sub> comprises -CH<sub>2</sub>-, -alkylene-, -alkenylene-, -alkylene-S-, -S-alkylene-, -alkylene-O-, -O-alkylene-, -alkylene-S(O)<sub>2</sub>-, -S(O)<sub>2</sub>-alkylene, -O-, -N(R<sub>15</sub>)-, -C(O)-, -CON(R<sub>15</sub>)-, -N(R<sub>15</sub>)C(O)-, -N(R<sub>15</sub>)CON(R<sub>16</sub>)-, -N(R<sub>15</sub>)C(O)O-, -OC(O)N(R<sub>15</sub>)-, -N(R<sub>15</sub>)SO<sub>2</sub>-, -SO<sub>2</sub>N(R<sub>15</sub>)-, -C(O)-O-, -O-C(O)-, -S-, -S(O)-, -S(O<sub>2</sub>)-, -N(R<sub>15</sub>)SO<sub>2</sub>N(R<sub>16</sub>)-,



wherein R<sub>13</sub>, R<sub>15</sub>, R<sub>16</sub>, and R<sub>17</sub> independently comprise: -hydrogen, -alkyl, -aryl, -heteroaryl, -arylene-alkyl, -heteroarylene-alkyl, -alkylene-aryl, -alkylene-heteroaryl, -alkylene-arylene-alkyl, or -alkylene-heteroarylene-alkyl;

25 D<sub>2</sub> comprises -CH<sub>2</sub>-, -alkylene-, -alkenylene-, -alkylene-S-, -S-alkylene-, -alkylene-O-, -O-alkylene-, -alkylene-S(O)<sub>2</sub>-, -S(O)<sub>2</sub>-alkylene, -O-, -N(R<sub>25</sub>)-, -C(O)-, -CON(R<sub>25</sub>)-, -N(R<sub>18</sub>)C(O)-, -N(R<sub>18</sub>)CON(R<sub>19</sub>)-, -N(R<sub>18</sub>)C(O)O-, -OC(O)N(R<sub>18</sub>)-, -N(R<sub>18</sub>)SO<sub>2</sub>-, -SO<sub>2</sub>N(R<sub>18</sub>)-, -C(O)-O-, -O-C(O)-, -S-, -S(O)-, -S(O<sub>2</sub>)-, -N(R<sub>18</sub>)SO<sub>2</sub>N(R<sub>19</sub>)-, and

30 wherein R<sub>18</sub> and R<sub>19</sub> independently comprise: -hydrogen, -alkyl, -aryl, -arylene-alkyl, -alkylene-aryl, or -alkylene-arylene-alkyl; and

R<sub>14</sub> comprises -hydrogen, -alkyl, -aryl, -heteroaryl, -arylene-alkyl, -heteroarylene-alkyl, -alkylene-aryl, -alkylene-heteroaryl, -alkylene-arylene-alkyl, or -alkylene-heteroarylene-alkyl.

5           12. The compound of Formula (I) in claim 1, wherein Ar<sub>1</sub> comprises a mono-substituted phenyl group wherein the substituent comprises: -aryl, -arylene-alkyl, -D<sub>1</sub>-aryl, -D<sub>1</sub>-alkylene-arylene-alkyl, or -arylene-D<sub>1</sub>-alkyl;

wherein

10           D<sub>1</sub> comprises -O-, -N(R<sub>11</sub>)-, -CON(R<sub>11</sub>)-, or -N(R<sub>11</sub>)C(O)-, and wherein R<sub>11</sub> comprises: -hydrogen; -alkyl; or -aryl.

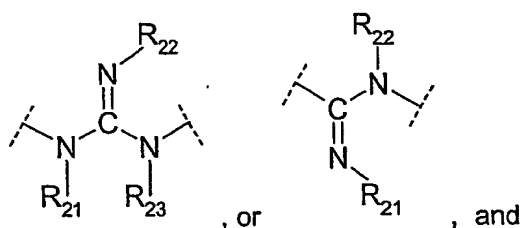
13. The compound of Formula (I) in claim 1, wherein Ar<sub>2</sub> comprises a phenyl, naphthyl, pyridyl, isoquinolyl, pyrimidyl or quinazolyl group optionally substituted 1 to 7 times.

15           14. The compound of Formula (I) in claim 1, wherein Ar<sub>2</sub> comprises a substituted phenyl, 2-naphthyl, 2-pyridyl, 3-isoquinolyl, 2-pyrimidyl or 2-quinazolyl group having 1 to 5 substituents wherein the substituents independently comprise:

- a) -fluoro;
- b) -chloro;
- 20 c) -bromo;
- d) -iodo;
- e) -cyano;
- f) -nitro;
- g) -perfluoroalkyl;
- 25 h) -T<sub>1</sub>-R<sub>20</sub>;
- i) -alkyl;
- j) -aryl;
- k) -heteroaryl;
- l) -heterocyclyl;
- 30 m) -cycloalkyl;
- n) -alkylene-aryl;
- o) -alkylene-arylene-aryl;
- p) -alkylene-arylene-alkyl;
- q) -arylene-alkyl;
- 35 r) -arylene-aryl;
- s) -arylene-heteroaryl;
- t) -heteroarylene-aryl;

- u) -heteroarylene-heteroaryl;  
v) -heteroarylene-heterocyclyl  
w) -arylene-heterocyclyl  
x) -arylene-arylene-alkyl;  
5 y) - T<sub>1</sub>-alkyl;  
z) - T<sub>1</sub>-aryl;  
aa) - T<sub>1</sub>-alkylene-aryl;  
bb) - T<sub>1</sub>-alkenylene-aryl;  
cc) - T<sub>1</sub>-alkylene-heteroaryl;  
10 dd) - T<sub>1</sub>-alkenylene-heteroaryl;  
ee) - T<sub>1</sub>-cycloalkylene-aryl;  
ff) - T<sub>1</sub>-cycloalkylene-heteroaryl;  
gg) -T<sub>1</sub>-heterocyclylene-aryl;  
hh) -T<sub>1</sub>-heterocyclylene-heteroaryl;  
15 ii) - T<sub>1</sub>-arylene-alkyl;  
jj) - T<sub>1</sub>-arylene-alkenyl;  
kk) - T<sub>1</sub>-alkylene-arylene-aryl;  
ll) - T<sub>1</sub>-arylene-T<sub>2</sub>-aryl;  
mm) - T<sub>1</sub>-arylene-arylene-aryl;  
20 nn) - T<sub>1</sub>-alkylene-arylene-alkyl;  
oo) -alkylene-T<sub>1</sub>-alkylene-aryl;  
pp) -arylene-T<sub>1</sub>-alkyl;  
qq) -arylene-T<sub>1</sub>-alkylene-aryl;  
rr) -T<sub>1</sub>-alkylene-T<sub>2</sub>-aryl;  
25 ss) -T<sub>1</sub>-alkylene-aryl;  
tt) -alkylene-T<sub>1</sub>-heteroaryl;  
uu) -alkylene-T<sub>1</sub>-cycloalkyl;  
vv) -alkylene-T<sub>1</sub>-heterocyclyl;  
ww) -alkylene-T-arylene-alkyl;  
30 xx) -alkylene-T<sub>1</sub>-alkylene-arylene-alkyl;  
yy) -alkylene-T<sub>1</sub>-alkyl;  
zz) -alkylene-T<sub>1</sub>-R<sub>20</sub>;  
aaa) -arylene- T<sub>1</sub>-R<sub>20</sub>; or  
bbb) -hydrogen;  
35 wherein

T<sub>1</sub> comprises -CH<sub>2</sub>-, -O-, -N(R<sub>21</sub>)-, -C(O)-, -CON(R<sub>21</sub>)-, -N(R<sub>21</sub>)C(O)-, -N(R<sub>21</sub>)CON(R<sub>22</sub>)-, -N(R<sub>21</sub>)C(O)O-, -OC(O)N(R<sub>21</sub>)-, -N(R<sub>21</sub>)SO<sub>2</sub>-, -SO<sub>2</sub>N(R<sub>21</sub>)-, -C(O)-O-, -O-C(O)-, -S-, -S(O)-, -S(O<sub>2</sub>)-, -N(R<sub>21</sub>)SO<sub>2</sub>N(R<sub>22</sub>)-,



5 wherein R<sub>20</sub>, R<sub>21</sub>, R<sub>22</sub> and R<sub>23</sub>, independently comprise: -hydrogen, -alkyl, -alkenyl, -alkylene-cycloalkyl, -alkynene-heterocyclyl, -aryl, -heteroaryl, -arylene-alkyl, -alkylene-aryl, -alkylene-arylene-alkyl, -alkylene-arylene-aryl, -alkylene-arylene-alkylene-aryl, -alkylene-arylene-O-arylene, or alkylene-arylene-O-alkylene-aryl; and

10 T<sub>2</sub> comprises a direct bond, -CH<sub>2</sub>-, -O-, -N(R<sub>24</sub>)-, -C(O)-, -CON(R<sub>24</sub>)-, -N(R<sub>24</sub>)C(O)-, -N(R<sub>24</sub>)CON(R<sub>25</sub>)-, -N(R<sub>24</sub>)C(O)O-, -OC(O)N(R<sub>24</sub>)-, -N(R<sub>24</sub>)SO<sub>2</sub>-, -SO<sub>2</sub>N(R<sub>24</sub>)-, -C(O)-O-, -O-C(O)-, -S-, -S(O)-, -S(O<sub>2</sub>)-, -N(R<sub>24</sub>)SO<sub>2</sub>N(R<sub>25</sub>)-, wherein R<sub>24</sub> and R<sub>25</sub> independently comprise; -hydrogen, -alkyl, -alkenyl, -alkylene-cycloalkyl, alkynene-heterocyclyl, -aryl, -heteroaryl, -arylene-alkyl, -alkylene-aryl, and -alkylene-arylene-alkyl.

15

15. The compound of Formula (I) in claim 1, wherein Ar<sub>2</sub> comprises a substituted phenyl, 2-naphthyl, 2-pyridyl, 3-isoquinolyl, 2-pyrimidyl or 2-quinazolyl group having 1 to 5 substituents independently comprising:

- 20 a) -fluoro;  
 b) -chloro;  
 c) -bromo;  
 d) -iodo;  
 e) -cyano;  
 25 f) -nitro;  
 g) -perfluoroalkyl;  
 h) -T<sub>1</sub>-R<sub>20</sub>;  
 i) -alkyl;  
 j) -aryl;  
 30 k) -arylene-alkyl;  
 l) -T<sub>1</sub>-alkyl;  
 m) -T<sub>1</sub>-alkylene-aryl;

- n) -T<sub>1</sub>-alkylene-arylene-aryl;
- o) -T<sub>1</sub>-alkylene-arylene-alkyl;
- p) -arylene-T<sub>1</sub>-alkyl; or
- q) -hydrogen;

5 wherein

T<sub>1</sub> comprises -CH<sub>2</sub>-, -O-, -N(R<sub>21</sub>)-, -CON(R<sub>21</sub>)-, or -N(R<sub>21</sub>)C(O)-; wherein R<sub>20</sub> and R<sub>21</sub> independently comprise: -hydrogen, -alkyl, or -aryl.

16. The compound of Formula (I) in claim 1,

10 wherein

c is equal to 0;

G comprises: -hydrogen or -CO<sub>2</sub>H;

V comprises: -CH<sub>2</sub>- or a direct bond;

X comprises: -CON(R<sub>8</sub>)-, or -N(R<sub>8</sub>)CO-;

15 wherein R<sub>8</sub> comprises: -hydrogen;

Ar<sub>1</sub> comprises a mono-substituted phenyl group

wherein

the substituent comprises: -aryl, -arylene-alkyl, -D-aryl, -D-alkylene-arylene-alkyl, or -arylene-D-alkyl,

20 wherein D comprises -O-, or -N(R<sub>11</sub>)-,

wherein R<sub>11</sub> comprises: -hydrogen, -alkyl, or -aryl;

Ar<sub>2</sub> comprises a substituted phenyl, 2-naphthyl, 2-pyridyl, 3-isoquinolyl, 2-pyrimidyl or 2-quinazolyl group having 1 to 5 substituents independently comprising: -fluoro, -

chloro, -bromo, iodo, -cyano, -nitro, -perfluoroalkyl, -T-R<sub>14</sub> -alkyl, -aryl, -arylene-alkyl,

25 -T-alkyl, -T-alkylene-aryl, -T-alkylene-arylene-aryl, -T-alkylene-arylene-alkyl, -arylene-T-alkyl;

wherein

T comprises -CH<sub>2</sub>-, -O-, -N(R<sub>15</sub>)-, -CON(R<sub>15</sub>)-, or -N(R<sub>15</sub>)C(O)-;

wherein

30 R<sub>14</sub> and R<sub>15</sub> independently comprise: -hydrogen, -alkyl, or -aryl; and

wherein

the alkyl, aryl, alkylene, and arylene groups in Ar<sub>1</sub> and Ar<sub>2</sub> may be optionally substituted

1 to 4 times with a substituent group, wherein said substituent group(s) or the term

substituted refers to groups comprising: -hydrogen, -fluoro, -chloro, -bromo, iodo, -

35 cyano, -nitro, -perfluoroalkyl.

17. The compound of Formula (I) in claim 1, wherein Ar<sub>1</sub> comprises:



2'-phenoxy-biphenyl-4-yl, 2'-(4-methoxy-phenoxy)-biphenyl-4-yl, 2'-(4-pentyl-phenoxy)-biphenyl-4-yl, 2'-(4-tert-butyl-phenoxy)-biphenyl-4-yl, 2'-(4-trifluoromethoxy-phenoxy)-biphenyl-4-yl, 2'-Benzyloxy-biphenyl-4-yl, 2-Biphenyl-4-yl, 2'-cyclopentyloxy-biphenyl-4-yl, 2'-hydroxy-biphenyl-4-yl, 2'-isopropoxy-biphenyl-4-yl, 2'-phenoxy-biphenyl-4-yl, 2'-piperidin-1-ylmethyl-biphenyl-4-yl, 2'-trifluoromethyl-biphenyl-4-yl, 3',4',5'-trimethoxy-biphenyl-4-yl, 3',4'-dichloro-biphenyl-4-yl, 3',5'-Bis-trifluoromethyl-biphenyl-4-yl, 3'-Chloro-4'-fluoro-biphenyl-4-yl, 3'-methoxy-biphenyl-4-yl, 3'-nitro-biphenyl-4-yl, 3'-trifluoromethyl-biphenyl-4-yl, 3'-Acetylamino-biphenyl-4-yl, 3'-Benzyloxy-biphenyl-4-yl, Biphenyl-4-yl, 3'-Chloro-4'-fluoro-biphenyl-4-yl, 3-chloro-4-fluorophenoxy-biphenyl-4-yl, 3-fluoro-phenoxy-biphenyl-4-yl, 3-hydroxy-4-nitro-phenoxy, 3-hydroxy-4-nitro-phenoxy-phenyl, 3'-methoxy-biphenyl-4-yl, 3'-nitro-biphenyl-4-yl, 3'-phenoxy-biphenyl-4-yl, 3'-trifluoromethyl-biphenyl-4-yl, 4-(4'-Cyano-phenoxy)-phenyl, 4-(4'-Nitro-phenoxy)-phenyl, 4-(4'-Trifluoromethyl-phenoxy)-phenyl, 4'-(Acetylamino-methyl)-biphenyl-4-yl, 4'-cyclohexyl-biphenyl-4-yl, 4'-methoxy-biphenyl-4-yl, 4'-Nitro-biphenyl-4-yl, 4'-trifluoromethyl-biphenyl-4-yl, 4'-Trifluoromethyl-biphenyl-4-yl, 4'-Amino-biphenyl-4-yl, 4'-Chloro-biphenyl-4-yl, 4-Cyano-phenoxy)-phenyl, 4'-cyclohexyl-biphenyl-4-yl, 4'-Dimethylamino-biphenyl-4-yl, 4-Formyl-phenoxy)-phenyl, 4'-Methanesulfonylamino-biphenyl-4-yl, 4'-methoxy-biphenyl-4-yl, 4-methoxy-phenoxy)-biphenyl-4-yl, 4'-pentyl-biphenyl-4-yl, 4'-phenoxy-biphenyl-4-yl, 4-Pyridin-4-yl-phenyl, 4-tert-Butyl-benzyloxy)-biphenyl-4-yl, 4'-tert-Butyl-biphenyl-4-yl, 4-tert-Butyl-phenoxy)-biphenyl-4-yl, 4-Thiophen-3-yl-phenyl, 4'-trifluoromethoxy-biphenyl-4-yl, 4-trifluoromethyl-phenoxy)-biphenyl-4-yl, 4-trifluoromethyl-phenoxy)-biphenyl-4-yl, 5'-Chloro-2'-methoxy-biphenyl-4-yl, 5'-Fluoro-2'-methoxy-biphenyl-4-yl, 5-nitro-biphenyl-3-carboxylic acid methyl ester, or 5-Phenyl-pyridin-2-yl, 6-phenyl-pyridin-3-yl, 4'-cyano-biphenyl-4-yl.

18. The compound of Formula (I) in claim 1, wherein X comprises -CON(R<sub>8</sub>)- or -N(R<sub>8</sub>)CO- wherein R<sub>8</sub> comprises hydrogen, (1-Acetyl-(2R)-pyrrolidin-2-yl)-methyl, (1-cyclopentanecarbonyl-(2S)-pyrrolidin-2-yl)-methyl, (biphenyl-4-carbonyl)-(2-biphenyl-4-yl-1-carboxy)-ethyl, 1-(2-methanesulfonyl-benzenesulfonyl)-(2R)-pyrrolidin-2-ylmethyl, 2-(1-methyl-1H-imidazole-4-sulfonylamino)-ethyl, 1-(2,2-dimethyl-propionyl)-(2S)-pyrrolidin-2-ylmethyl, 2-methanesulfonyl-benzenesulfonyl, 1-(2-thiophen-2-yl-acetyl)-(2R)-pyrrolidin-2-ylmethyl, 4-methanesulfonyl-benzenesulfonyl, 1-(4-methanesulfonyl-benzenesulfonyl)-(2R)-pyrrolidin-2-ylmethyl, 2-(1,2-dimethyl-1H-imidazole-4-sulfonylamino)-ethyl, 1-Acetyl-(2S)-pyrrolidin-2-ylmethyl, 1-cyclopentanecarbonyl-(2S)-pyrrolidin-2-ylmethyl, 2-(2-Acetylamino-4-methyl-thiazole-5-sulfonylamino)-ethyl, 2-(5-chloro-1,3-dimethyl-1H-pyrazole-4-sulfonylamino)-ethyl, 2-(2-methanesulfonyl-benzenesulfonylamino)-ethyl, 2-(3,5-dimethyl-isoxazole-4-sulfonylamino)-ethyl, 2-(4-methanesulfonyl-benzenesulfonylamino)-ethyl, 2-(5-chloro-1,3-dimethyl-1H-pyrazole-4-sulfonylamino)-ethyl, 2-(2,4-dimethoxy-benzylamino)-

ethyl, 2-Amino-ethyl, 2-hydroxy-benzyl, (2-methanesulfonyl-benzenesulfonylamino)-ethyl, 2-tert-butoxycarbonylamino-ethyl, (2-thiophen-2-yl-acetyl)-pyrrolidine-2-methyl, 4-chloro-benzyl, 4-isopropyl-benzyl, 5-tert-butyl-2-hydroxy-benzyl, naphthalen-1-yl-methyl.

19. The compound of Formula (I) in claim 1 comprising (2S)-[(Isoquinoline-3-carbonyl)-amino]-3-(3;5'-bistrifluoromethyl-biphenyl-4-yl)-propionic acid.

20. The compound of Formula (I) in claim 1 comprising 3-Biphenyl-4-yl-(2S)-[[7-(3-chloro-4-fluoro-phenyl)-isoquinoline-3-carbonyl]-amino]-propionic acid.

21. The compound of Formula (I) in claim 1 comprising 3-Biphenyl-4-yl-(2S)-[[6-(3-chloro-4-fluoro-phenyl)-pyridine-2-carbonyl]-amino]-propionic acid.

22. The compound of Formula (I) in claim 1 comprising 3-Hydroxy-naphthalene-2-carboxylic acid (2-biphenyl-4-yl-ethyl)-amide.

23. The compound of Formula (I) in claim 1 comprising (2S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(3'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester.

24. The compound of Formula (I) in claim 1 comprising (2S)-[(3'-Chloro-4'-fluoro-4-hydroxy-biphenyl-3-carbonyl)-amino]-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid methyl ester.

25. The compound of Formula (I) in claim 1 comprising (2S)-[5-Bromo-2(4-trifluoromethyl-benzyloxy)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid.

26. The compound of Formula (I) in claim 1 comprising 3-Biphenyl-4-yl-(2S)-[5-bromo-2-(4-tert-butyl-benzyloxy)-benzoylamino]-propionic acid.

27. The compound of Formula (I) in claim 1 comprising (2S)-[5-Bromo-2(4-phenyl-butoxy)-benzoylamino]-3-(4'-phenoxy-biphenyl-4-yl)-propionic acid.

28. The compound of Formula (I) in claim 1 comprising 3-Biphenyl-4-yl-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid.

29. The compound of Formula (I) in claim 1 comprising 3-Biphenyl-4-yl-(2S)-[(3'-chloro-4'-fluoro-biphenyl-4-carbonyl)-amino]-propionic acid.

30. The compound of Formula (I) in claim 1 comprising 3-Biphenyl-4-yl-(2S)-[(4'-trifluoromethoxy-biphenyl-4-carbonyl)-amino]-propionic acid.
31. The compound of Formula (I) in claim 1 comprising 3-Biphenyl-4-yl-(2S)-[(4'-tert-butyl-4-chloro-biphenyl-3-carbonyl)-amino]-propionic acid.
- 5        32. The compound of Formula (I) in claim 1 comprising 3-(4'-Trifluoromethyl-biphenyl-4-yl)-(2S)-[4-(4-trifluoromethyl-phenoxy)-benzoylamino]-propionic acid.
33. The compound of Formula (I) in claim 1 comprising (2S)-[(4'-Trifluoromethoxy-biphenyl-4-carbonyl)-amino]-3-(4'-trifluoromethyl-biphenyl-4-yl)-propionic acid.
- 10       34. The compound of Formula (I) in claim 1 comprising 3-(4'-Trifluoromethoxy-biphenyl-4-yl)-(2S)-[(4'-trifluoromethyl-biphenyl-4-carbonyl)-amino]-propionic acid.
35. The compound of Formula (I) in claim 1 comprising 3-Biphenyl-4-yl-(2S)-[[4(4-tert-butyl-benzoylamino)-3'-chloro-4'-fluoro-biphenyl-3-carbonyl]-amino]-propionic acid.
- 15       36. The compound of Formula (I) in claim 1 comprising 3-Biphenyl-4-yl-(2S)-[5-bromo-2-(4-tert-butyl-benzenesulfonylamino)-benzoylamino]-propionic acid.
37. The compound of Formula (I) in claim 1 comprising (2S)-{5-Chloro-2-[(naphthalen-1-ylmethyl)-amino]-benzoylamino}-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid.
- 20       38. The compound of Formula (I) in claim 1 comprising 2S-[5-Chloro-2-(2methyl-butylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid.
39. The compound of Formula (I) in claim 1 comprising (2S)-[5-Chloro-2(3-chloro-4-fluoro-phenylamino)-benzoylamino]-3-(2'-phenoxy-biphenyl-4-yl)-propionic acid.
- 25       40. A pharmaceutical composition comprising a therapeutically effective amount of the compound of Formula (I) as claimed in claim 1, and one or more pharmaceutically acceptable carriers, excipients, or diluents.
- 30       41. The pharmaceutical composition of claim 40, wherein the compound of Formula (I) is an antagonist of factor IX activity.

42. The pharmaceutical composition of claim 41, wherein the compound of Formula (I) is a partial antagonist of factor IX activity, wherein a partial antagonist comprises a compound that inhibits less than complete activity at a physiologically tolerable dose.

5 43. The pharmaceutical composition of claim 42, wherein the compound of Formula (I) inhibits up to 95% of factor IX activity.

44. The pharmaceutical composition of claim 42, wherein the compound of Formula (I) inhibits up to 80% of factor IX activity.

45. The pharmaceutical composition of claim 42, wherein the compound of Formula (I) inhibits up to 50% of factor IX activity.

10 46. The pharmaceutical composition of claim 41, wherein the compound of Formula (I) antagonizes blood clotting mediated by factor IX.

47. The pharmaceutical composition of claim 40, wherein said therapeutically effective amount comprises a sufficient amount of the compound of Formula (I) to at least partially inhibit the biological activity of factor IX in a subject.

15 48. The pharmaceutical composition of claim 40 wherein said therapeutically effective amount of Formula (I) comprises a sufficient amount of the compound of Formula (I) to at least partially inhibit the intrinsic clotting cascade in a subject.

20 49. The pharmaceutical composition of claim 48, wherein said therapeutically effective amount of Formula (I) preferentially inhibits the intrinsic clotting cascade as compared to the extrinsic clotting cascade.

50. The pharmaceutical composition of claim 48, wherein said therapeutically effective amount of Formula (I) inhibits the intrinsic clotting cascade by greater than 80% and inhibits the extrinsic clotting cascade by less than 50%.

25 51. The pharmaceutical composition of claim 40, wherein said therapeutically effective amount of Formula (I) comprises a sufficient amount of the compound of Formula (I) for at least partial amelioration of at least one factor IX-mediated disease.

52. The pharmaceutical composition of claim 40 in the form of an oral dosage or parenteral dosage unit.

53. The pharmaceutical composition of claim 40, wherein said compound of Formula (I) is administered as a dose in a range from about 0.01 to 1,000 mg/kg of body weight per day.

54. The pharmaceutical composition of claim 40, wherein said compound of Formula (I) is administered as a dose in a range from about 0.1 to 100 mg/kg of body weight per day.

55. The pharmaceutical composition of claim 40, wherein said compound of Formula (I) is administered as a dose in a range from about 0.5 to 10 mg/kg of body weight per day.

56. The pharmaceutical composition of claim 51, wherein said factor IX-mediated disease comprises stroke.

57. The pharmaceutical composition of claim 51, wherein said factor IX-mediated disease comprises deep vein thrombosis.

58. The pharmaceutical composition of claim 57, wherein said thrombosis is associated with surgical procedures, long periods of confinement, acquired or inherited pro-coagulant states including anti-phospholipid antibody syndrome, protein C deficiency and protein S deficiency, or acute and chronic inflammation including recurrent miscarriage or Systemic Lupus Erythmatosis (SLE).

59. The pharmaceutical composition of claim 51, wherein said factor IX-mediated disease comprises excessive clotting associated with the treatment of kidney diseases by hemodialysis and/or venous hemofiltration.

60. The pharmaceutical composition of claim 51, wherein said factor IX-mediated disease comprises cardiovascular disease.

61. The pharmaceutical composition of claim 40, wherein said cardiovascular disease comprises myocardial infarction, arrhythmia, or aneurysm.

62. The pharmaceutical composition of claim 40, wherein said composition is used to replace or supplement compounds that reduce clotting.

63. The pharmaceutical composition of claim 40 further comprising one or more therapeutic agents.

64. A method for the inhibition of the normal biological function of factor IX comprising administering to a subject in need thereof a compound of Formula (I) as claimed in claim 1.

65. The method of claim 64, wherein said compound of Formula (I) is administered to said subject as a pharmaceutical composition comprising a therapeutically effective amount of said compound of Formula (I) and one or more pharmaceutically acceptable carriers, excipients, or diluents.

5           66. The method of claim 64, wherein the compound of Formula (I) is an antagonist of factor IX activity.

67. The method of claim 64, wherein said compound of Formula (I) is a partial antagonist of factor IX, wherein a partial antagonist comprises a compound that inhibits less than complete activity at a physiologically tolerable dose.

10           68. The method of claim 67, wherein said compound of Formula (I) inhibits up to 95% of factor IX activity.

69. The method of claim 67, wherein said compound of Formula (I) inhibits up to 80% of factor IX activity.

15           70. The method of claim 67, wherein said compound of Formula (I) inhibits up to 50% of factor IX activity.

71. The method of claim 64, wherein the compound of Formula (I) antagonizes blood clotting mediated by factor IX.

20           72. The method of claim 64, wherein said compound of Formula (I) is administered in an amount sufficient to partially antagonize the biological activity of factor IX in said subject.

73. The method of claim 65, wherein said therapeutically effective amount of the compound of Formula (I) comprises a sufficient amount of the compound of Formula (I) to at least partially inhibit the intrinsic clotting cascade in said subject.

25           74. The method of claim 65, wherein said therapeutically effective amount of Formula (I) preferentially inhibits the intrinsic clotting cascade as compared to the extrinsic clotting cascade.

75. The method of claim 65, wherein said therapeutically effective amount of Formula (I) inhibits the intrinsic clotting cascade by greater than 80% and inhibits the extrinsic clotting cascade by less than 50%.

76. The method of claim 65, wherein said therapeutically effective amount of the compound of Formula (I) comprises a sufficient amount of the compound of Formula (I) for treatment or prevention of factor IX-mediated diseases.

5 77. The method of claim 64, wherein said pharmaceutical composition is administered in the form of an oral dosage or parenteral dosage unit.

78. The method of claim 64, wherein said compound of Formula (I) is administered as a dose in a range from about 0.01 to 1,000 mg/kg of body weight per day.

79. The method of claim 64, wherein said compound of Formula (I) is administered as a dose in a range from about 0.1 to 100 mg/kg of body weight per day.

10 80. The method of claim 64, wherein said compound of Formula (I) is administered as a dose in a range from about 0.5 to 10 mg/kg of body weight per day.

81. The method of claim 76, wherein said factor IX-mediated disease comprises stroke.

15 82. The method of claim 76, wherein said factor IX-mediated disease comprises deep vein thrombosis.

83. The method of claim 82, wherein said thrombosis is associated with surgical procedures, long periods of confinement, acquired or inherited pro-coagulant states including anti-phospholipid antibody syndrome, protein C deficiency and protein S deficiency, or acute and chronic inflammation including recurrent miscarriage or Systemic Lupus Erythmatosis (SLE).

20

84. The method of claim 76, wherein said factor IX-mediated disease comprises clotting associated with the treatment of kidney disease by hemodialysis and/or venous hemofiltration.

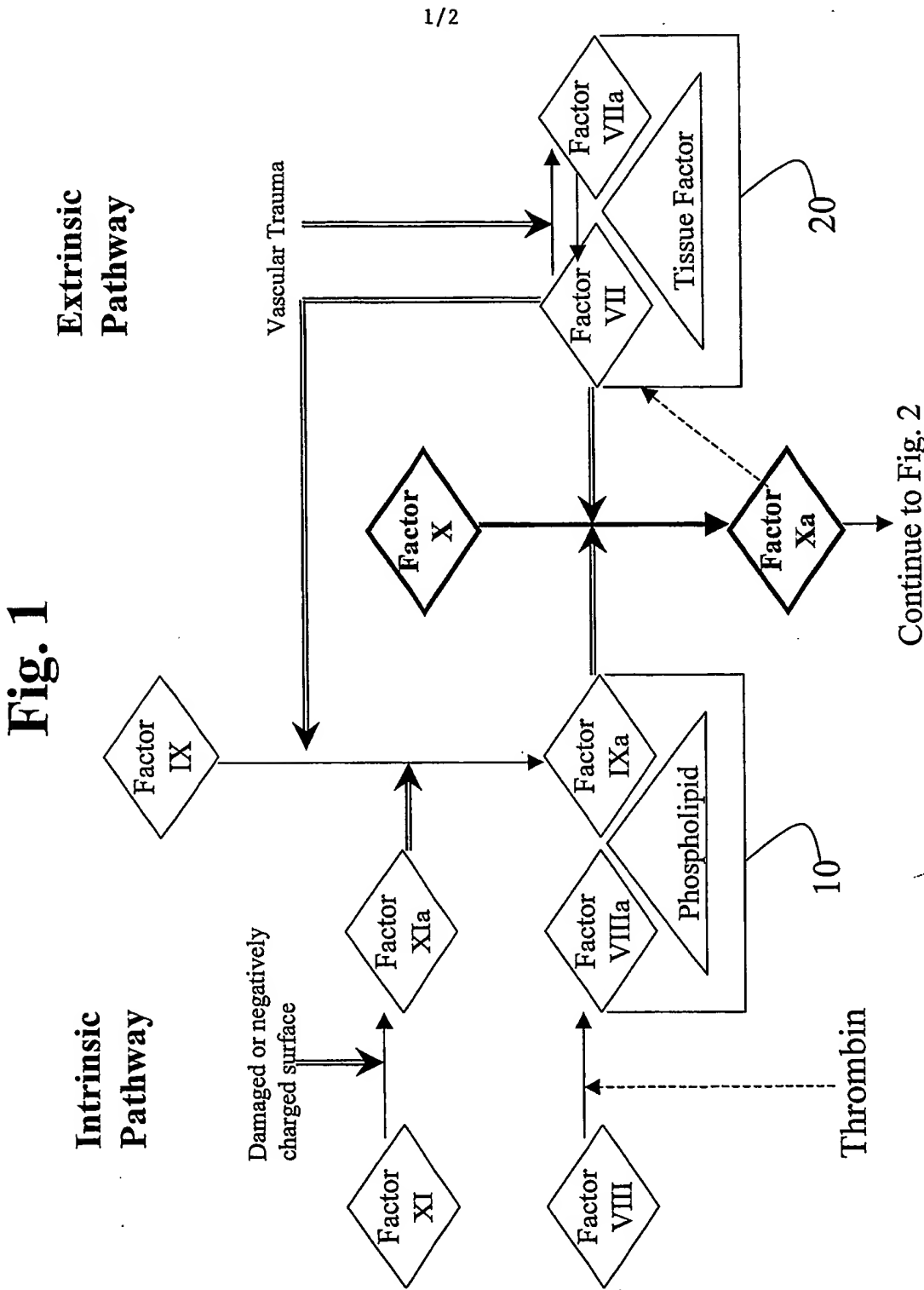
25 85. The method of claim 76, wherein said factor IX-mediated disease comprises cardiovascular disease.

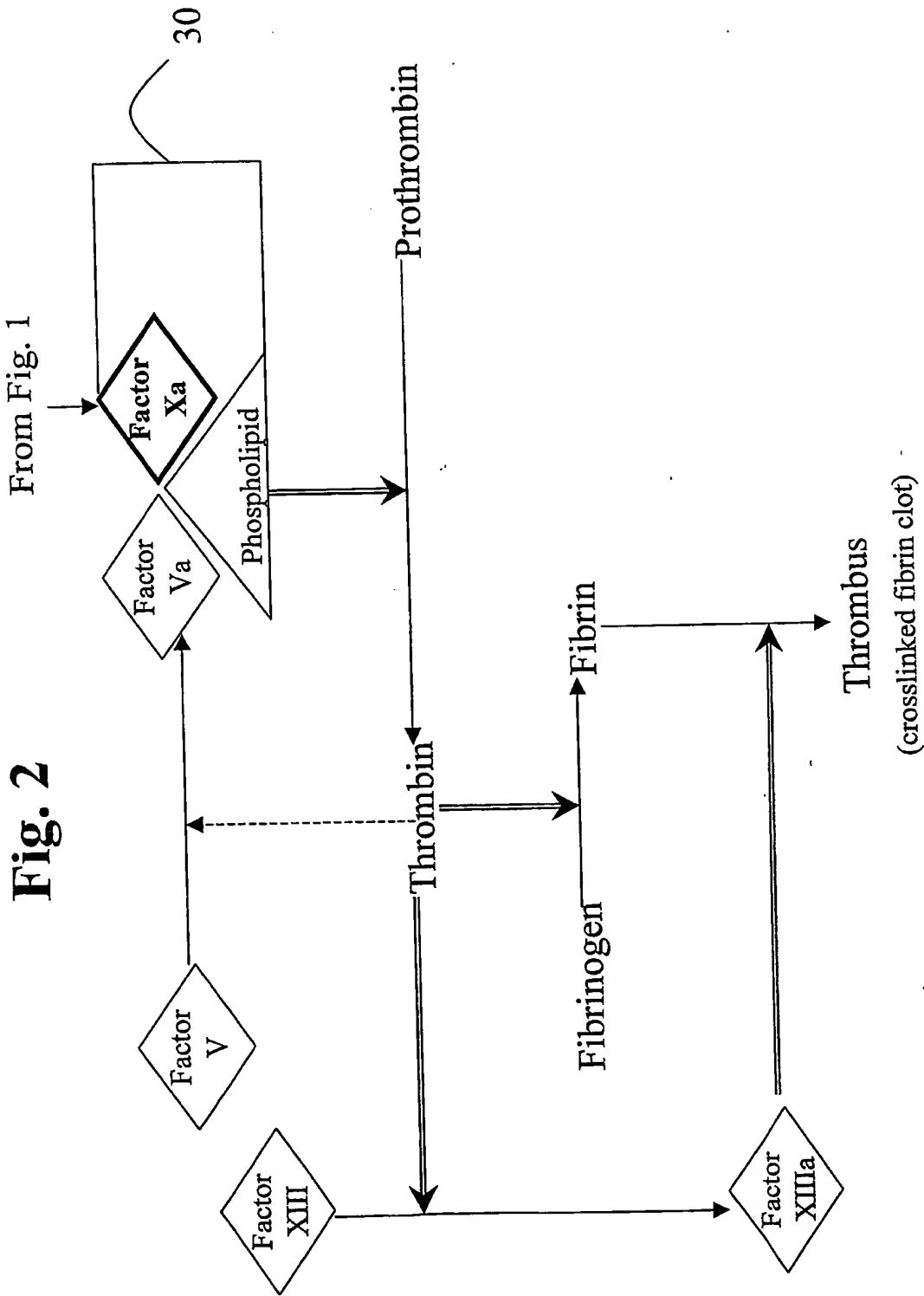
86. The method of claim 85, wherein said cardiovascular disease comprises myocardial infarction, arrhythmia, or aneurysm.

87. The method of claim 64, wherein said compound of Formula (I) is used to replace or supplement compounds that reduce clotting.

88. The method of claim 65, wherein said pharmaceutical composition further comprises one or more therapeutic agents.







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